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Original Article

Effect of adding biologic agents to disease-modifying anti-rheumatic drugs for refractory chronic suppurative otitis media: comparative outcomes and cytokine-driven mechanisms

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Abstract: Objective: To evaluate systematically the efficacy of disease-modifying anti-rheumatic drugs (DMARDs) versus DMARDs plus biologics for refractory chronic suppurative otitis media (rCSOM), and to explore changes in systemic cytokine levels as surrogate markers of inflammatory modulation. Methods: This retrospective study included 102 rCSOM patients (2020-2025). Patients were divided into a DMARDs-alone (DMA) group and a DMARDs-plus-biologics (Combined) group. Using 1:1 propensity score matching, 40 patients were included in each group. Primary outcome: otorrhea cessation rate at 12 weeks. Secondary outcomes: hearing levels, including the pure tone average (PTA) and speech discrimination score (SDS); cytokine levels, including C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α); and quality of life, assessed using the Zurich Chronic Middle Ear Inventory (ZCMEI-21). Multivariate logistic regression was used to adjust for confounders. Adverse reactions were recorded. Results: At week 12 of treatment, the otorrhea cessation rate was markedly higher in the Combined group than the DMA group (P<0.05). The Combined group also had a lower PTA and lower CRP, IL-6, TNF-α levels, as well as lower ZCMEI-21 scores, but higher SDS values (all P<0.05). Multivariate logistic regression showed combination therapy was an independent protective factor for otorrhea cessation (OR=3.850, 95% CI: 1.101-13.466, P=0.035), while baseline CRP was an independent negative predictor of otorrhea cessation (OR=0.425, 95% CI: 0.268-0.672, P<0.001). The incidence of adverse events did not differ between groups (P=0.644). Conclusion: Combining DMARDs with biologics improves outcomes in rCSOM compared to DMARDs alone, with a favorable safety profile. Baseline CRP independently predicts treatment response. Although the proposed mechanism is inferred from systemic cytokines in the absence of mucosal evidence, these findings support salvage immunomodulatory therapy and warrant future tissue-based validation.

Keywords: Antirheumatic agents, biologic agents, refractory chronic suppurative otitis media, salvage therapy, autoimmunity

Introduction

Refractory Chronic Suppurative Otitis Media (rCSOM) is a chronic middle ear infection persisting for more than two months that is refractory to conventional treatment. Its clinical management is extremely challenging [1]. The core pathologic feature of this disease is tympanic membrane perforation with persistent or intermittent otorrhea, which often leads to progressive hearing loss [2]. Without effective control, inflammation may spread to adjacent structures, causing serious complications, including tympanic sclerosis, cholesteatoma formation, labyrinthitis, facial nerve paralysis, and even intracranial infections such as meningitis or brain abscess [3]. Even with conservative treatment, patients with rCSOM may still exhibit persistent purulent ear discharge [4]. The predominant pathogens in rCSOM are *Pseudomonas aeruginosa* and *Staphylococcus aureus* [5]. Historically, streptomycin and other antibiotics significantly reduced the need for surgery in patients with temporal bone osteomyelitis [6]. However, the widespread use of antibiotics has altered pathogen profiles and antimicrobial

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resistance patterns, necessitating continuous monitoring and regular follow-up [7]. Acetic acid ear irrigation is an important conservative management strategy prior to surgical intervention, aimed at maintaining a dry ear [8].

DMARDs and biologic agents work primarily by modulating the immune system and regulating inflammatory responses. Biologic agents comprise monoclonal antibodies, fusion proteins, and nanobodies. They suppress the inflammatory cascade by targeting specific cytokines or immune cells. Anti-tumor necrosis factor (TNF) biologics have been successfully used to treat rheumatoid arthritis, managing disease progression by inhibiting TNF-α [9]. In inflammatory bowel disease (IBD), anti-TNF agents target macrophages and other immune cells, thereby suppressing the production of pro-inflammatory cytokines [10]. IL-12/IL-23 inhibitors exert an inhibitory effect on the production of downstream pro-inflammatory cytokines by blocking key cytokines in the T helper 1 (Th1) and T helper 17 (Th17) cell differentiation pathways. IL-17 inhibitors target IL-17 produced by Th17 cells to alleviate inflammatory responses [10]. Pro-inflammatory cytokines are the core mediators of the inflammatory pathway. IL-6 regulates IL-17A expression through the signal transducer and activator of transcription 3 (STAT3) pathway, while IL-17A activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)/mitogen-activated protein kinase (MAPK) pathway through the IL-17RA receptor, collectively amplifying the inflammatory response [11]. Moreover, the genetic polymorphisms of cytokines can alter their expression levels, thereby affecting the intensity of inflammatory responses and disease progression. Overactivation of pro-inflammatory cytokine genes or insufficient expression of anti-inflammatory cytokine genes can lead to the formation of a chronic inflammatory microenvironment [12]. In chronic otitis media (COM), cytokines hold a central position in driving pathophysiologic changes. IL-1α and TNF-α exert regulatory effects on bone resorption associated with COM [13]. In otitis media with effusion (OME), the assessment of IL-1 receptor antagonists and immunomodulatory IL-10 levels in middle ear fluid can help understand its pathogenesis [14]. Unlike pro-inflammatory mediators such as TNF-α, IL-1, and IL-6, the anti-inflammatory cytokine IL-10 mitigates inflammatory conditions such as rheumatoid arthritis and is associated with a reduced risk of osteoporosis [15]. Although there is limited systematic research on the direct use of biologics for rCSOM, biologics have shown potential in treating eosinophilic otitis media (EOM), a disease that is also difficult to treat with conventional therapies [16]. According to a systematic review and meta-analysis of biotherapy efficacy in eosinophilic otitis media, biologics may serve as an effective treatment, especially for steroid-nonresponsive patients [17]. Biologic agents such as rituximab (an anti-CD20 monoclonal antibody) have been used to treat refractory recurrent polychondritis, which is an autoimmune disease that has not responded to other treatments [18]. These successes suggest that biologics may also be effective in rCSOM treatment.

Against this background, the present study was designed to assess the efficacy of biologics in combination with DMARDs versus DMARDs monotherapy for the treatment of rCSOM, and to explore preliminarily the changes in systemic cytokine levels as surrogate markers of inflammation, while acknowledging that direct local mechanisms remain to be investigated. A retrospective controlled clinical study was conducted to compare the two therapeutic regimens comprehensively in terms of their effects on otorrhea relief, hearing improvement, inflammatory cytokine levels, and patients' quality of life. The aim was to objectively demonstrate the utility of biologics in rCSOM treatment, provide a scientific basis for establishing precision treatment strategies for CSOM based on immune regulation, and ultimately improve patient prognosis and reduce disease burden.

Patients and methods

Study subjects

This was a retrospective cohort study, and data collection and analysis were independently conducted by researchers who were not involved in patient management. We enrolled 102 rCSOM patients treated between January 2020 and March 2025. Based on the treatment regimen, patients were divided into two groups: 49 patients who received DMARDs monotherapy were included in the DMARDs monotherapy group (DMA group); 53 patients treated with a combination of DMARDs and

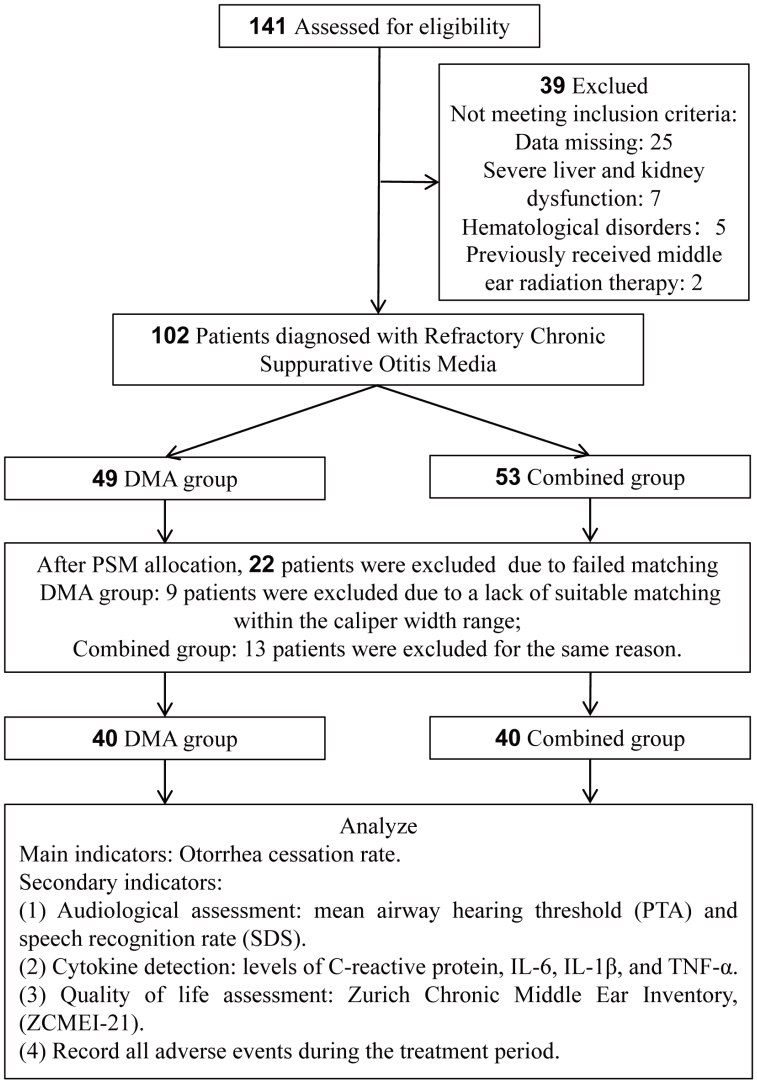

Figure 1. Research flow chart. 102 rCSOM patients were initially enrolled and divided into two groups: DMA group (DMARDs monotherapy, n=49) and Combined group (DMARDs plus biologics, n=53). After 1:1 propensity score matching (PSM), 40 patients remained in each group. Among the 49 DMA group patients, 9 were excluded due to lack of suitable match within the caliper width; among the 53 Combined group patients, 13 were similarly excluded. No other exclusions occurred. Abbreviations: rCSOM, refractory chronic suppurative otitis media; DMA, DMARDs monotherapy; Combined, DMARDs combined with biologics.

biologics were included in the combined treatment group (Combined group).

To minimize confounding bias, we performed 1:1 nearest-neighbor propensity score matching (PSM) without replacement [19]. Propensity scores were estimated using a logistic regression model incorporating the following baseline covariates: age, sex, disease duration, baseline hearing level (PTA), and baseline CRP level. A caliper width of 0.2 standard deviations (SD) of the logit of the propensity score was applied to restrict the maximum allowable difference between matched pairs. Balance was assessed using standardized mean differences (SMD), with an SMD <0.1 considered indicative of adequate balance. No additional weighting correction was applied post-matching. None of the initial 102 patients were excluded due to missing data, as all enrolled participants had complete records for the matched variables and outcome measures. Consequently, all 102 patients proceeded directly to PSM. Following matching, no missing data were present for any outcome variable among the 80 included patients (**Figure 1**).

Inclusion criteria

(1) Age ≥18 years; (2) Met the diagnostic criteria of rCSOM: persistent otorrhea for more than 8 weeks, ineffective after standardized antibacterial treatment (including local ear drops and systemic antibiotic use for ≥2 weeks) or prior tympanoplasty failure [20]; (3) Ear endoscopy revealed tympanic membrane perforation with purulent discharge; (4) Pure Tone Audiometry (PTA) examination confirms conductive or mixed hearing loss; (5) High-resolution CT of the temporal bone shows signs of COM and mastoiditis, with no evidence of cholesteatoma; (6) Complete clinical data were available, including ear endoscopy examination records, audiologic evaluations, laboratory test results, and treatment records; (7) The patient provided informed consent and signed a written consent form.

Exclusion criteria

(1) Concomitant acute suppurative otitis media, cholesteatoma type otitis media, or malignant tumor of the middle ear; (2) History of

congenital malformation of the outer and middle ear or temporal bone fracture; (3) Severe hepatic or renal dysfunction (ALT or AST >3 times the upper limit of normal, creatinine >177 μmol/L) or hematologic disorders; (4) Pregnant or lactating women; (5) Previously received middle ear radiation therapy; (6) Incomplete result data.

Ethical statement

This study adhered to the principles of the Helsinki Declaration [21] and was approved by the Ethics Committee of The First Affiliated Hospital of Henan University of Chinese Medicine (approval No. 2025HL-782-01). All patients were informed of the research objectives, treatment plans, and potential risks, and signed informed consent forms. Identifiable patient data were retained for clinical monitoring.

Sample size estimation

This retrospective study used G*Power 3.1 software for sample size estimation [22]. Based on previous studies [23], we assumed a Cohen's d effect size of 0.5, a significance level of α=0.05 (two-sided), and a statistical power of 1 - β = 0.90. These parameters required 34 participants, and a total of 80 participants were included in this study, exceeding the required sample size. Post-hoc power analysis was performed using G*Power 3.1 software based on the primary endpoint (otorrhea cessation rate at 12 weeks) of this study. The results showed that with an effect size of 0.52, α=0.05 (two-sided), and a total sample size of 80 cases after PSM matching, the actual statistical power (1-β) of this study was 0.92, which was higher than the recommended standard of 0.80 for clinical studies, indicating that the sample size was sufficient to minimize type II error risk and that the statistical inferences were reliable.

Treatment measures

Both groups received standardized local treatment. Under otoscopic guidance, the external auditory canal and middle ear cavity were gently cleaned using sterile suction to remove purulent discharge and debris once daily before ear drop instillation. Ofloxacin ear drops (0.3%, 5 drops per instillation) were then instilled with the patient with the affected ear upward for 10 minutes, three times daily, for 12 consecutive weeks.

In addition, the DMARDs monotherapy group (n=40) received methotrexate tablets (2.5 mg/tablet) administered orally at a fixed dose of 15 mg once weekly (taken as a single dose on the same day each week) for 12 weeks. No dose adjustment was permitted during the study period. Folic acid 5 mg/week was given 24 hours after methotrexate to reduce gastrointestinal and hepatic adverse events. Treatment was interrupted if any of the following occurred: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× upper limit of normal, white blood cell count <3.0× 10^9/L, or grade 3/4 adverse events according to CTCAE v5.0. Interrupted cases were excluded from the efficacy analysis but included in the safety assessment.

The combination therapy group (n=40) received, in addition to the same methotrexate regimen, adalimumab injection (40 mg/0.8 mL) administered subcutaneously with an initial loading dose of 80 mg in week 1 (40 mg on day 1 and another 40 mg on day 4), followed by 40 mg every two weeks thereafter, for a total of 12 weeks [24]. No dose adjustment of adalimumab was allowed. Interruption criteria for adalimumab were: severe injection site reaction (grade ≥3), systemic hypersensitivity, or active infection requiring systemic antibiotics.

Neither group received any other immunomodulators, glucocorticoids, or systemic antibiotics during the 12-week treatment period. Patients who required treatment interruption or additional medications were documented as protocol deviations and were not included in the final efficacy analysis.

Observation indicators

Main indicators: Otorrhea cessation rate: evaluated through otoscopy, defined as the absence of purulent discharge at the site of tympanic membrane perforation and a dry ear condition lasting ≥7 days. Evaluations were performed at 12 weeks of treatment.

Secondary indicators: (1) Audiological assessment: A Madsen Astera2 pure tone audiometer

Table 1. Baseline characteristics [mean ± SD, n (%)]

Variable	DMA group (*n*=40)	Combined group (*n*=40)	χ^2/t	*95% CI*	*P*	*SMD*
Female	21 (52.5)	22 (55.0)	0.050	-	0.823	0.05
Age (years)	44.3±3.8	44.0±2.9	0.361	-1.242, 1.792	0.719	0.09
BMI	23.5±2.8	22.5±2.4	1.688	-0.180, 2.185	0.096	0.08
Duration of illness (months)	9.3±3.5	8.9±3.3	0.514	-1.128, 1.913	0.609	0.02
Smoking History	6 (15.0)	4 (10.0)	0.457	-	0.499	0.02
Alcohol history	5 (12.5)	3 (7.5)	0.139	-	0.709	0.02
Hypertension	3 (7.5)	2 (5.0)	0.213	-	0.644	0.01
Hyperlipidemia	2 (5.0)	1 (3.5)	0.346	-	0.556	0.07
Diabetes mellitus	3 (7.5)	3 (7.5)	0.000	-	1.000	0.01
Allergic rhinitis	7 (17.5)	7 (17.5)	0.230	-	0.632	0.01
PTA (dB)	48.6±7.3	47.9±6.8	0.488	-2.476, 4.086	0.627	0.09
SDS (%)	69.9±5.2	69.4±5.8	0.406	-1.960, 2.965	0.686	0.09
CRP (mg/L)	9.7±2.4	9.5±2.2	0.276	-0.869, 1.149	0.783	0.08
IL-6 (pg/mL)	18.4±3.8	17.9±3.7	0.530	-1.212, 2.092	0.597	0.03
IL-1β (pg/mL)	3.6±1.1	3.7±1.2	0.416	-0.638, 0.418	0.679	0.01
TNF-α (pg/mL)	16.9±3.6	16.5±4.1	0.466	-1.309, 2.109	0.643	0.01
ZCMEI-21	29.8±2.5	29.4±2.1	0.825	-0.601, 1.451	0.412	0.07

Note: BMI: Body Mass Index; CI: Confidence Interval; PTA: Pure tone average hearing threshold; SDS: Speech recognition rate; CRP: C-reactive protein; IL: interleukin; TNF: Tumor Necrosis Factor; ZCMEI-21: Zurich Chronic Middle Ear Inventory-21. Continuous variables are presented as the mean ± SD and were compared using the independent-samples t-test. Categorical variables are presented as n (%) and were compared using the Chi-square test.

was used for pure tone audiometry, and the average air conduction hearing threshold (PTA) at frequencies of 0.5, 1, 2, and 4 kHz is calculated [4]. The GSI 61 dual channel diagnostic audiometer was used for speech recognition rate (SDS) testing [25], with a test intensity of 30 dB HL above the patient's comfort threshold, and the percentage of correct recognition was recorded.

(2) Cytokine detection: Five milliliters of peripheral venous blood were collected, serum was centrifuged, and an enzyme-linked immunosorbent assay was used to detect. C-reactive protein (CRP) (kit: R&D Systems, Catalog # DCRP00), interleukin-6 (IL-6) (R&D Systems, Catalog # D6050), IL-1β (R&D Systems, Catalog # DLB50), and tumor necrosis factor alpha (TNF-α) (R&D Systems, Catalog # DTA00D) levels. All procedures were performed strictly in accordance with the manufacturer's instructions.

(3) The Zurich Chronic Middle Ear Inventory (ZCMEI-21) [26, 27] is an internationally recognized disease-specific quality of life assessment tool designed specifically for patients with COM.

(4) Adverse reaction monitoring: All adverse events were recorded during the treatment period.

Statistical analysis

Data analysis was performed using SPSS 25.0. Kolmogorov-Smirnov test and Q-Q plots were used to assess normality, and Levene's test was used to assess variance homogeneity. Normally distributed data were presented as mean ± standard deviation. Independent-samples t-test was used for between-group comparison, and repeated-measures ANOVA for temporal interaction analysis. Categorical data were expressed as n (%), compared by the chi-square test. Multivariate logistic regression was applied to screen independent influencing factors. A *P*-value <0.05 was defined as statistical significance.

Results

Baseline characteristics

Baseline characteristics of the two rCSOM patient cohorts are compared in **Table 1**. After PSM, all covariates had an SMD <0.1, indicat-

Table 2. Comparison of otorrhea cessation rates [n (%)]

	DMA group (*n*=40)	Combined group (*n*=40)	χ^2	*P*	*OR (95% CI)*
Resolved	20 (50.0)	29 (72.5)	4.266	0.039	2.636 (1.040-6.685)
Unresolved	20 (50.0)	11 (27.5)			

Note: The otorrhea cessation rates were tested using Chi-square test. OR (odds ratio) and its 95% CI were calculated based on binary logistic regression with treatment plan as the independent variable.

Table 3. Comparison of PTA and SDS (mean ± SD)

	DMA group (*n*=40)	Combined group (*n*=40)	*t*	*95% CI*	*P*
PTA (dB)					
Baseline	48.6±7.3	47.9±6.8	0.488	-2.476, 4.086	0.627
After treatment	37.9±7.9	32.3±7.9	3.168	2.081, 9.119	0.002
ΔPTA	-10.9±2.2	-15.6±2.3	9.344	-5.817, -3.773	<0.001
	P-Time <0.001	P-Group <0.001	P-Time*Group <0.001		
SDS (%)					
Baseline	69.9±5.2	69.4±5.8	0.406	-1.960, 2.965	0.686
After treatment	77.3±5.8	80.7±6.4	2.496	-6.107, -0.688	0.015
ΔSDS	7.5±2.4	11.4±2.5	7.266	-4.969, -2.831	<0.001
	P-Time <0.001	P-Group <0.001	P-Time*Group <0.001		

Note: CI: Confidence Interval; PTA: Pure tone average hearing threshold; SDS: Speech recognition rate; Δ denotes the change from baseline (post-treatment minus baseline values). Data are expressed as the mean ± SD. A paired t-test was used for within-group comparisons, and an independent-samples t-test was used for between-group comparisons. Time effects, between-group effects, and interaction effects were analyzed using a two-way repeated-measures ANOVA.

ing good balance, and no significant intergroup differences were observed (all P>0.05).

Comparison of otorrhea cessation rate

In **Table 2**, After 12 weeks of treatment, the otorrhea cessation rate in the Combined group was 72.5% (29/40), significantly higher than the 50.0% (20/40) in the DMARDs monotherapy group (χ^2=4.266, P=0.039).

Improvement in hearing function

In **Table 3**, Pretreatment PTA and SDS showed no inter-group differences (P>0.05). At 12 weeks post-treatment, the Combined group had a lower PTA (P=0.002) and a higher SDS (P=0.015) than the DMA group, with significantly greater improvements in both indices (P<0.001). Repeated-measures analysis revealed that the *P*-values for the time, intergroup, and interaction effects were all <0.01, indicating divergent temporal trends in PTA and SDS between the two groups. Overall, DMARDs combined with biologics led to greater improvement in patients' hearing function compared to DMARDs monotherapy.

Changes in cytokine levels

Table 4 shows pre-/post-treatment cytokine changes in two groups. Baseline CRP, IL-6, IL-1β, and TNF-α did not differ between groups (P>0.05); all were lower in the Combined group at week 12 (P<0.001). By repeated measurement analysis, the *P*-values for time, intergroup, and interaction effects were all <0.01, indicating that there were differences in the trend in cytokine changes over time between the two groups of patients. These findings suggest the superior anti-inflammatory effects of combination therapy.

Changes in quality of life

Table 5 compares pre-/post-treatment ZCMEI-21 scores between the two groups. Baseline scores showed no inter-group difference (P=0.439). At week 12, the Combined group had lower scores and greater improvements (both P<0.001). Repeated measurement analysis revealed that *P*-values for time, intergroup, and interaction effects were all <0.01, indicating a difference in the trend of ZCMEI-21 scores over time between the two groups of patients. Combination therapy was more effective than

Table 4. Comparison of immunoinflammatory markers (mean ± SD)

		DMA group (*n*=40)	Combined group (*n*=40)	*t*	*95% CI*	*P*
CRP (mg/L)	Baseline	9.7±2.4	9.5±2.2	0.276	-0.869, 1.149	0.783
	After treatment	3.6±1.0	2.76±0.7	4.300	0.446, 1.215	<0.001
		P-Time <0.001	P-Group <0.001		P-Time*Group <0.001	
IL-6 (pg/mL)	Baseline	18.4±3.8	17.9±3.7	0.530	-1.212, 2.092	0.597
	After treatment	3.36±0.5	2.72±0.6	5.144	0.392, 0.888	<0.001
		P-Time <0.001	P-Group <0.001		P-Time*Group <0.001	
IL-1β (pg/mL)	Baseline	3.55±1.1	3.67±1.2	0.416	-0.638, 0.418	0.679
	After treatment	0.39±0.1	0.28±0.2	3.602	0.049, 0.171	<0.001
		P-Time <0.001	P-Group <0.001		P-Time*Group <0.001	
TNF-α (pg/mL)	Baseline	16.86±3.6	16.46±4.1	0.466	-1.309, 2.109	0.643
	After treatment	3.37±0.5	3.01±0.5	3.285	0.145, 0.591	<0.001
		P-Time <0.001	P-Group <0.001		P-Time*Group <0.001	

Note: CI: Confidence Interval; CRP: C-reactive protein; IL: interleukin; TNF: Tumor Necrosis Factor. The data were expressed as mean ± SD. Independent-samples t-test was used for inter group comparison. Time effects, between-group effects, and interaction effects were analyzed using a two-way repeated-measures ANOVA.

Table 5. Comparison of ZCMEI-21 score (mean ± SD)

	DMA group (*n*=40)	Combined group (*n*=40)	*t*	*95% CI*	*P*
Baseline	29.8±2.5	29.4±2.1	0.825	-0.601, 1.451	0.412
After treatment	23.2±2.4	20.5±2.3	5.065	1.624, 3.726	<0.001
ΔZCMEI-21	6.6±3.1	8.9±2.4	3.617	-3.489, -1.011	<0.001
	P-Time <0.001	P-Group <0.001		P-Time*Group <0.001	

Note: CI: Confidence Interval; ZCMEI-21: Zurich Chronic Middle Ear Inventory-21. Δ denotes the change from baseline (post-treatment minus baseline values). The data are expressed as mean ± SD. Paired t-test is used for intra group comparison before and after, and independent-samples t-test is used for inter group comparison. Time effects, between-group effects, and interaction effects were analyzed using a two-way repeated-measures ANOVA.

DMARDs monotherapy in improving quality of life.

Adverse reactions

Table 6 shows ARs during treatment: 3 cases (7.5%, hepatic dysfunction and gastrointestinal symptoms) in the DMA group vs. 2 (5.0%, injection site reactions) in the Combined group. The incidence of adverse events did not differ (χ^2=0.213, P=0.644). All adverse reactions were mild to moderate and resolved with symptomatic treatment; no severe events or treatment discontinuation occurred.

Multivariate logistic regression analysis

In **Table 7**, Univariate logistic regression analysis was conducted, with the cessation of otorrhea treatment at 12 weeks as the dependent variable (1 = cessation, 0 = non cessation) with treatment plan (0 = DMA group, 1= Combined group), age, duration of illness, baseline PTA, baseline CRP, and other independent variables. The results showed that combination therapy, age, and baseline CRP levels were independent influencing factors for the cessation of otorrhea after 12 weeks of treatment (all P<0.05).

In **Table 8**, in order to further eliminate various systematic biases and confounding factors, the above variables were included in a multivariate logistic regression model. The results showed that the combination therapy was an independent protective factor for the cessation of otorrhea after 12 weeks of treatment. The probability of otorrhea cessation with DMARDs plus biologics was 3.85-fold higher than with DMARDs monotherapy (OR=3.850, 95% CI: 1.101-13.466, P=0.035); CRP is also a significant independent predictor, with a corresponding 57.5% lower probability of otorrhea

Table 6. Comparison of adverse events [n (%)]

	DMA group (*n*=40)	Combined group (*n*=40)	χ^2	*P*
Abnormal liver function	2 (5.0)	0 (0)		
Gastrointestinal discomfort	1 (2.5)	0 (0)		
Injection site reaction	0 (0)	2 (5.0)		
Overall	3 (7.5)	2 (5.0)	0.213	0.644

Note: The data are represented as n (%). The overall incidence of adverse reactions was compared between groups using Chi-square test.

Table 7. Binary logistic regression analysis of otorrhea cessation

Variables	B	SE	Wald	P	OR	95% CI for OR	
						Lower limits	Upper limits
Combination therapy	0.969	0.475	4.169	0.041	2.636	1.04	6.685
Famale	0.140	0.460	0.093	0.760	1.151	0.467	2.835
Age	-0.196	0.078	6.406	0.011	0.822	0.706	0.957
BMI	-0.012	0.086	0.021	0.885	0.988	0.835	1.169
Duration of illness	-0.054	0.068	0.640	0.424	0.947	0.829	1.082
Smoking	-0.993	0.692	2.060	0.151	0.370	0.095	1.438
Alcohol	0.059	0.769	0.006	0.939	1.061	0.235	4.790
Hypertension	-0.923	0.944	0.958	0.328	0.397	0.062	2.524
Hyperlipidemia	-1.197	1.247	0.921	0.337	0.302	0.026	3.481
Diabetes mellitus	-0.496	0.851	0.340	0.560	0.609	0.115	3.227
Allergic rhinitis	1.548	0.803	3.717	0.054	4.703	0.975	22.692
Baseline PTA	-0.02	0.032	0.400	0.527	0.980	0.921	1.043
Baseline SDS	0.058	0.044	1.766	0.184	1.060	0.973	1.155
Baseline CRP	-0.781	0.189	17.082	<0.001	0.458	0.316	0.663
Baseline IL-6	-0.053	0.063	0.700	0.403	0.948	0.838	1.074
Baseline IL-1β	0.188	0.198	0.900	0.343	1.207	0.818	1.779
Baseline TNF-α	-0.033	0.061	0.300	0.584	0.967	0.859	1.090
Baseline ZCMEI-21	-0.205	0.107	3.698	0.054	0.814	0.661	1.004

Note: Univariate binary logistic regression was used with whether the ear leak stopped at 12 weeks as the dependent variable (1 = stopped, 0 = not stopped). B: Regression coefficient; SE: Standard Error; Wald: Wald Chi-square value; OR: Odds Ratio; BMI: Body Mass Index; CI: Confidence Interval; PTA: Pure tone average hearing threshold; SDS: Speech recognition rate; CRP: C-reactive protein; IL: interleukin; TNF: Tumor Necrosis Factor; ZCMEI-21: Zurich Chronic Middle Ear Inventory-21.

cessation for every 1 mg/L increase in its concentration (OR=0.425, 95% CI: 0.268-0.672, P<0.001).

Discussion

The results showed that the 12-week otorrhea cessation rate in the combination therapy group was 72.5%, significantly higher than the 50.0% in the DMARDs monotherapy group. These findings indicate that the combination of biologics and DMARDs effectively reduced chronic inflammation in rCSOM patients. Persistent otorrhea is thought to result from the continuous secretion by the middle ear mucosa of inflammatory exudate under pathogen stimulation. TNF-α and IL-6 are key factors driving this process [28]. Adalimumab, as a humanized anti-TNF-α monoclonal antibody, can specifically bind to TNF-α, blocking its binding to receptors, thereby inhibiting downstream NF-κB signaling pathway activation, reducing vascular permeability and inflammatory cell infiltration [29]. Methotrexate has a synergistic effect with biologics by inhibiting dihydrofolate reductase, reducing T cell proliferation and cytokine release [30].

Several studies have demonstrated efficacy of biologics in immune-mediated ear disorders.

Table 8. Multivariate logistic regression analysis of otorrhea cessation

Variable	B	SE	Wald	*P*	OR	95% CI for OR	
						Lower limits	Upper limits
Combination therapy	1.348	0.639	4.455	0.035	3.850	1.101	13.466
Age	0.042	0.134	0.100	0.752	1.043	0.803	1.356
Baseline CRP	-0.856	0.234	13.378	<0.001	0.425	0.268	0.672
Constant	6.452	5.199	1.540	0.215	633.662	-	-

Note: Include variables with P<0.10 in univariate analysis (combination therapy, age, baseline CRP) into a multivariate binary logistic regression model. B: Regression coefficient; SE: Standard Error; Wald: Wald Chi-square value; OR: Odds Ratio; CI: Confidence interval. Model goodness of fit test: χ^2=6.927 P=0.545, Nagelkerke R^2=0.482.

Anti-TNF agents improved cochlear blood flow and hearing thresholds in animal models [31, 32], and biologics were effective in eosinophilic otitis media [16, 17]. Unlike these reports, our study directly compared DMARDs monotherapy with DMARDs plus adalimumab in rCSOM. The greater clinical improvement in the combination group aligns with documented anti-TNF effects in other otologic conditions. Moreover, our cytokine data provided a mechanistic link not reported in previous studies, suggesting that systemic immunomodulation suppresses middle ear inflammation through the TNF-α/IL-6 axis.

Restoring hearing is one of the main therapeutic objectives of rCSOM treatment. In this study, the combination therapy group showed a significant decrease in PTA and a significant increase in SDS, indicating that immunomodulatory therapy contributed to hearing recovery. Although the pathogenesis of hearing impairment in rCSOM is multifactorial, our findings suggest a unifying immune-mediated pathway: inflammatory exudate accumulation, bacterial toxin infiltration, and labyrinthine inflammation converge on the TNF-α/IL-1β/inducible nitric oxide synthase (iNOS) axis. This mechanism parallels that of autoimmune sensorineural hearing loss and supports an immune-mediated pathogenesis for rCSOM. Thus, targeting this axis may concurrently control middle ear inflammation and prevent inner ear damage, offering a more comprehensive therapeutic approach than local treatment alone. The exotoxins and enzymes released by pathogens such as *Pseudomonas aeruginosa* can penetrate the round window membrane and enter the inner ear, directly damaging cochlear hair cells [1]. Sustained inflammatory response can activate the immune pathway within the labyrinth, leading to labyrinth inflammation and further exacerbating sensorineural hearing loss components [33].

Studies have shown that IL-1β and TNF-α upregulate iNOS expression, leading to nitric oxide (NO) overproduction and cochlear hair cell apoptosis. This mechanism has been validated in various hearing loss models, including noise-induced, drug-induced, and age-related hearing loss [34]. TNF-α not only directly participates in cytotoxic effects, but also damages cochlear microcirculation and exacerbates ischemic injury by regulating the contraction of spiral modiolar arteries [31]. Given the above mechanisms, targeting and blocking these inflammatory pathways has become a new strategy for protecting residual hearing. Biological agents, such as TNF-α inhibitor etanercept, have been shown to effectively alleviate cochlear inflammation. For example, in animal models, local application of TNF-α inhibitors can significantly improve cochlear blood flow after noise exposure and reduce the threshold of auditory brainstem response (ABR) [32]. Similarly, in the model of otitis media related hearing loss, inhibition of the TNF-α signaling pathway also showed protective effects on hair cells and improved ABR threshold [35]. Recent clinical data further confirm the effectiveness of this mechanism in humans. rCSOM patients receiving combination therapy with anti-inflammatory or immunomodulatory components showed significantly better hearing improvement than those receiving traditional treatment [36]. Additionalr studies support the use of anti-inflammatory drugs such as glucocorticoids as ototopical agents to treat CSOM, to control local inflammation and promote hearing recovery [37]. Subsequent studies should delve deeper into the clinical application potential of specific cytokine inhibitors in refractory otitis media.

We acknowledge that our mechanistic interpretation was based solely on peripheral blood cytokine measurements. Direct cellular or molecular evidence from middle ear mucosal tissue - such as local cytokine concentrations, immune cell phenotyping, or signaling pathway activation - was not obtained. Therefore, the proposed translational chain of "biologics - local immune regulation - otorrhea cessation" remains speculative and requires validation in future studies that incorporate tissue biopsies or middle ear fluid analysis. The present study clarified the core role of cytokine-driven mechanisms underlying the observed differences in therapeutic efficacy. After 12 weeks of treatment, the combination group exhibited markedly reduced CRP, IL-6, IL-1β, and TNF-α levels compared to the DMA group. IL-6, a multifunctional cytokine, participates in the maintenance of chronic inflammation in rCSOM by promoting B-cell differentiation and stimulating acute-phase protein synthesis [38]. Although tocilizumab was not administered in this study, adalimumab may indirectly lower IL-6 expression by inhibiting TNF-α, a key upstream inducer of IL-6 [39]. As a key upstream inflammatory initiator, IL-1β can induce the expression of multiple cellular adhesion molecules and facilitate neutrophil migration [40]. Multivariate analysis showed that baseline CRP was an independent negative predictor of otorrhea cessation, indicating that early use of enhanced immunotherapy in patients with high inflammatory status may improve prognosis [41]. Quality-of-life improvement is an important indicator of successful rCSOM treatment. This study used the ZCMEI-21 scale for evaluation, and the results showed a significant decrease in scores in the combination therapy group. Patients with rCSOM often experience anxiety and depression due to persistent otorrhea, hearing loss, and social dysfunction. Inflammatory cytokines act not only on local tissues but also on the central nervous system via the blood-brain barrier, inducing neurobehavioral changes [42]. TNF-α and IL-6 can activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to neurotransmitter imbalance [43]. Inhibition of these cytokines by biologic agents improves not only local symptoms but also overall quality of life.

The incidence of ARs did not differ significantly between the two groups in the present study, and both were mild to moderate, indicating that the combination of DMARDs with biologics is well-tolerated in rCSOM patients. Methotrexate, a cornerstone therapy for autoimmune diseases such as rheumatoid arthritis, is widely used clinically but is associated with significant adverse effects. Numerous studies have shown that the most common methotrexate-related adverse effects primarily involve the hepatic and gastrointestinal systems. A study on 325 patients with rheumatoid arthritis showed that the overall incidence of ARs related to methotrexate was as high as 34.2%, with gastrointestinal ARs being the most common, followed by liver function abnormalities indicated by elevated liver enzymes [44]. A retrospective study at a tertiary dermatology center in Malaysia also demonstrated that methotrexate use in psoriasis is associated with hepatotoxicity risk, manifested primarily as abnormal transaminase levels [45]. These findings collectively confirm that liver dysfunction and gastrointestinal reactions are the two most concerning toxic manifestations in methotrexate treatment. The primary safety concern with biologics is the increased risk of infection [33], arising from their core mechanism of action of biologics: regulating overactive immune responses by targeting and inhibiting key pro-inflammatory cytokines or immune cell pathways. However, while this immune regulatory effect suppresses pathologic inflammation, it may also weaken the body's normal defense ability against pathogenic microorganisms, thereby increasing susceptibility to infection. Our single-center design and moderate sample size (n=80 post-PSM) may limit generalizability. Clinicians should therefore view our results as preliminary evidence supporting combination immunomodulation in selected rCSOM patients, and multicenter prospective studies are needed to confirm these findings.

Study limitations

This study had several limitations. First, although the retrospective design reduced confounding bias through PSM, it could not completely eliminate selection bias. Second, the small single-center sample size limited the generalizability of the results; multicenter, large-sample prospective randomized controlled trials are needed for validation. Thirdly, the treatment period of this study was 12 weeks, and

long-term follow-up data were lacking to evaluate the long-term recurrence rate and hearing stability. Fourth, only one class of biologic agent (anti-TNF-α) was used, and the efficacy of other targeted drugs such as anti-IL-6 and anti-IL-1β needs to be explored. Fifth, and most importantly, our mechanistic inference was limited by the lack of cellular or molecular evidence from middle ear mucosal tissue. All cytokine data were derived from peripheral blood, which may not fully reflect local middle ear immune regulation. Consequently, we cannot establish a direct evidence chain linking biologic therapy to local otorrhea cessation by mucosal immunomodulation. Future research should combine mucosal biopsy or middle ear fluid analysis with molecular biology techniques to validate the proposed mechanism directly.

Conclusion

In rCSOM patients refractory to conventional therapy, adding a biologic to DMARDs significantly improved otorrhea cessation, hearing, cytokine profiles, and quality of life compared to DMARDs alone, without increased adverse events. Higher baseline CRP independently predicts a lower likelihood of otorrhea cessation. Although direct evidence from middle ear mucosa is absent, these results support systemic immunomodulation as a promising salvage approach. Future studies should incorporate local tissue analysis to establish the translational mechanism fully.

Disclosure of conflict of interest

None.

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