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REVIEW ARTICLE

Efficacy and safety of mepolizumab in the treatment of CRSwNP in the real-life setting: a review of the literature

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Abstract

Purpose The anti-IL-5 agent mepolizumab has been recently approved for the treatment of severe and treatment-resistant forms of type 2 chronic rhinosinusitis with nasal polyps. However, a review summarizing the results of real-life studies and comparing them to results from phase III clinical trials, SYNAPSE and MERIT, is still lacking.

Methods A search of all real-life studies published from 2019 to 2025 was conducted. Patients characteristics at baseline and 6 and 12 months after starting mepolizumab were extracted and compared to those from phase III trials: age, sex, comorbid eosinophilic asthma, and nonsteroidal antiinflammatory drugs-exacerbated respiratory disease (N-ERD), atopy, previous endoscopic sinus surgery (ESS), blood eosinophils count (BEC), NPS, sense of smell, SNOT-22, Lund-Mackay score, adverse events (AEs), and response to treatment.

Results 13 papers were included, encompassing an overall number of 608 patients. A higher rate of comorbid asthma and N-ERD, but a lower rate of previous ESS, was found in the real-life cohort. Despite higher BEC, sinonasal symptom scores were generally lower in the real-life population. Nonetheless, mepolizumab led to improvements in mean BEC, SNOT-22, NPS, sniffin' sticks identification test, and loss of smell VAS in a real-life setting. Comorbid N-ERD was associated with better NPS outcomes but worse SNOT-22 scores and olfactory function, while no significant differences were observed regarding asthma. AEs were reported by 14.0% of patients, with 1.5% discontinuing mepolizumab, while non-responders were 7.9%.

Conclusions Mepolizumab was safe and effective, even in a real-life scenario, with results similar to those observed in phase III clinical trials.

Keywords CRSwNP · Mepolizumab · Real-life review · Quality of life · Type-2 comorbidities

Introduction

Eosinophilic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) are both debilitating conditions that share a common underlying pathological mechanism, notably type 2 inflammation that is driven primarily by cytokines such as IL-4, IL-5, and IL-13 [1, 2]. Among these, IL-5 plays a pivotal role in the chemotaxis, activation, and survival of eosinophils both in nasal and pulmonary tissues [3, 4]. Based on this understanding, several monoclonal antibodies targeting the IL-5 pathway have been developed, including mepolizumab, benralizumab, and reslizumab. Mepolizumab and Reslizumab act by directly inhibiting IL-5, while benralizumab binds to the receptors localized on the surface of eosinophils and basophils [5]. In particular, mepolizumab is a fully humanized monoclonal antibody

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that exerts its effect by inhibiting the binding of IL-5 to its receptor, which is expressed on the surface of eosinophils and basophils. While all three are approved for the treatment of eosinophilic asthma, in Italy, only mepolizumab has received authorization from the Italian Medicines Agency (AIFA) for the treatment of CRSwNP in 2020. The phase III trials SYNAPSE and MERIT demonstrated that mepolizumab is both safe and effective in the treatment of patients with CRSwNP. In particular, the study showed significant improvements in several key outcomes, including blood eosinophil count (BEC), nasal polyp score (NPS), loss of smell as measured by the visual analogue scale (VAS), and overall quality of life as assessed through the SinoNasal Outcome Test-22 (SNOT-22), regardless from other type-2 comorbidities such as asthma and nonsteroidal antiinflammatory drugs-exacerbated respiratory disease (N-ERD). In addition, mepolizumab significantly reduced the need for rescue endoscopic sinus surgery (ESS), which has traditionally been considered a last-line strategy for patients with refractory sinonasal disease unresponsive to medical therapy alone [6, 7]. To date, only a limited number of studies have evaluated the impact of mepolizumab in real-life clinical settings. Likewise, a comprehensive review summarizing real-world outcomes remains lacking, as do studies comparing the effectiveness and safety profiles reported in phase III and phase IV investigations. This review aims to summarize and critically assess the real-world efficacy of mepolizumab in patients with CRSwNP after 6 and 12 months of anti-IL5 administration, focusing on key outcomes such as NPS, sense of smell, quality of life, and the need for rescue systemic corticosteroids (SCS) or ESS. Additionally, the safety profile of mepolizumab will be examined, with particular attention to changes in BEC and the occurrence of adverse events (AE). Finally, findings from this review will be compared with data reported in phase III trials, namely SYNAPSE and MERIT.

Materials and methods

A search of all published studies was performed using the PubMed database. Studies were independently identified by two authors (PO and GM) using keyword combinations and were included in the present article following the PRISMA checklist [8]. Exclusion criteria were as follows: case series including fewer than 10 patients; studies reporting fewer than two specific sinonasal outcome measures among SNOT-22, NPS, loss of smell VAS score, sense of smell assessment through a 16-item sniffin' sticks identification test (16-SSIT) or a University of Pennsylvania Smell Identification Test (UPSIT), and Lund-Mackay score (LMS); reports with potential overlap in patient populations; and articles that did not clearly distinguish the effects of mepolizumab from those of other biologic therapies.

From each of the included studies, patients' demographic and clinical characteristics at baseline and 6 and 12 months after starting mepolizumab were extracted, collected, and compared to those from phase III trials. Recorded data included: age, sex, comorbid asthma and N-ERD, atopy, history of previous ESS, BEC, NPS (range 0–8), SNOT-22 (range 0–110), sense of smell evaluated with VAS (range 0–10) and/or 16-SSIT (range 0–16), LMS (range 0–24), AEs, and response to treatment. Mepolizumab was administered subcutaneously at a dose of 100 mg every four weeks. Response to treatment was assessed in accordance with the EPOS/EUFOREA update on the indication and assessment of biologics in CRSwNP. Patients who did not demonstrate improvement in any of the five proposed criteria (NPS, SCS use, SNOT-22, sense of smell, and impact of other type-2 comorbidities) were classified as non-responders [9].

Demographic characteristics from phase IV studies were compared with data from the phase III clinical trials SYNAPSE and MERIT. In contrast, treatment outcomes were compared only with those from SYNAPSE, as the MERIT study reported results using the least squares mean method, which is not directly comparable with unadjusted mean changes reported in real-world studies. Descriptive and mean values were calculated with Microsoft® Excel (Version 16.52, Redmond, WA, USA). Paired Student's t-tests were used to evaluate within-group differences between pre- and post-treatment scores, while independent-sample t-tests were applied to compare outcomes between phase 3 and phase 4 studies.

Results

An initial literature search identified 256 articles. After applying the PRISMA checklist, 13 studies met the inclusion criteria and were included in the present review, as displayed in Fig. 1. Outcomes were assessed at 6 months in 3 studies [10–12], at both 6 and 12 months in 6 studies [13–18], and at 12 months in the remaining 4 studies [19–22]. Among the evaluated parameters, NPS was the only outcome reported in all 13 studies. Conversely, the SNOT-22 was reported in 12 studies, BEC in 11, loss of smell VAS score in 6, the assessment of sense of smell by an identification test in 5, and the LMS in 2 studies. AEs were documented in 11 studies.

- Demographic features

The total number of patients across the selected studies was 608, of whom 334 were male (54.9%), with a mean age of

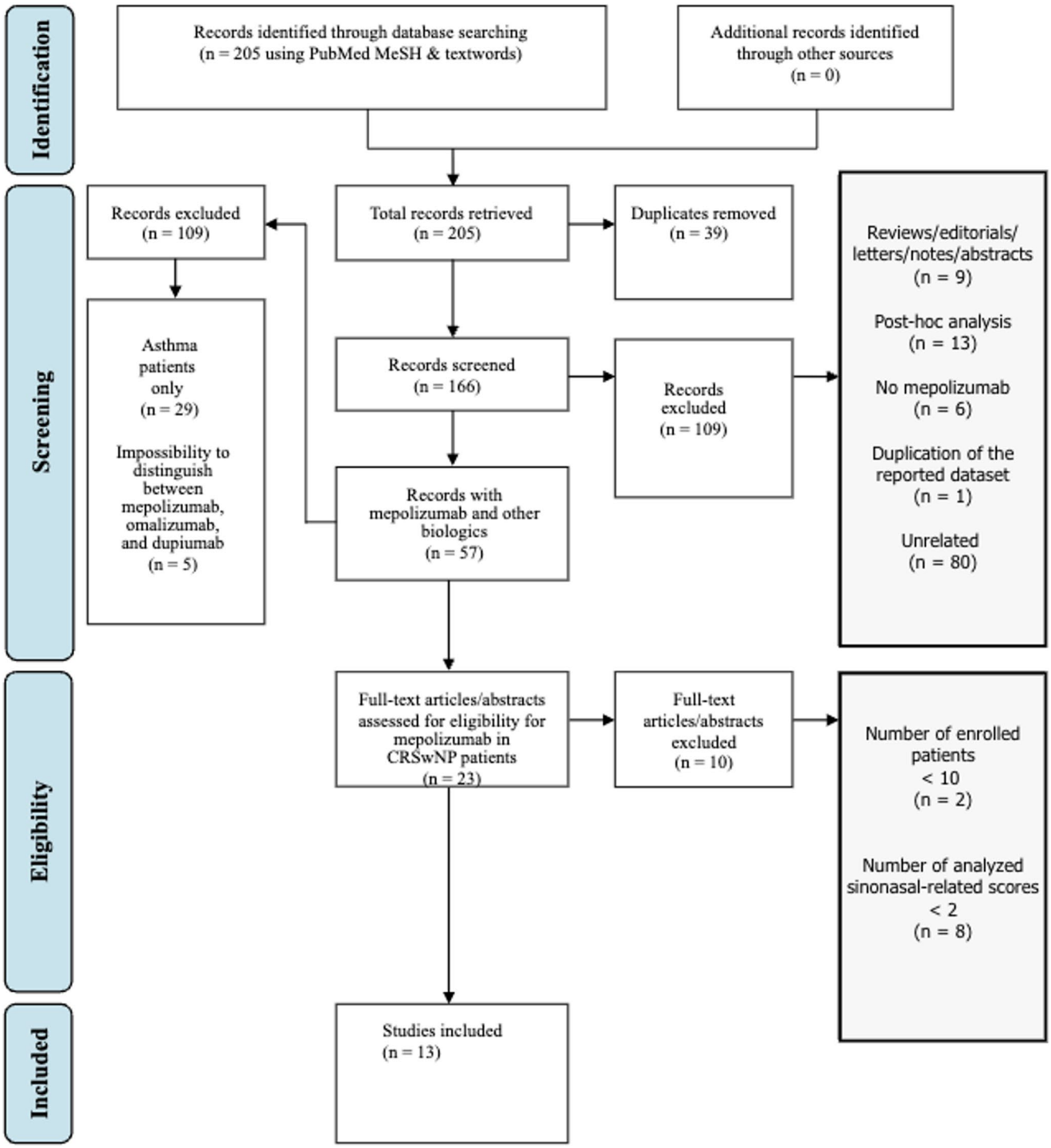

Fig. 1 PRISMA flow-chart

53.7 years. Regarding type 2 comorbidities, asthma and N-ERD were diagnosed in 482 (79.3%) and 187 (31.8%) patients, respectively, while 283 out of 474 patients (59.7%) had a documented history of atopy. Concerning surgical history, 501 out of 597 patients (83.9%) had undergone at least one previous ESS before starting anti-IL5 therapy.

A summary of the key characteristics from each study is presented in Table 1. For comparison, the phase III clinical trials SYNAPSE and MERIT collectively enrolled 286 patients. The proportion of male patients was higher (59.4%), and the mean age was lower, at 49.3 years. The prevalence of comorbid asthma and N-ERD was lower in

the phase III trials, 71.3% and 23.8%, respectively, whereas data on atopy were not reported. Finally, 258 out of 286 patients (90.2%) had a history of at least one previous ESS.

- Baseline scores

At baseline, the mean BEC in the real-life studies was 552.1 cells/μL, compared to 392.8 cells/μL in the two phase III trials. Despite this higher eosinophilic burden, sinonasal symptom scores were generally lower in the real-life population than in the phase III cohorts. Specifically, mean SNOT-22 scores were 57.6 in real-life studies versus 61.8 in phase III trials; mean nasal polyp scores NPS were 4.7 versus 5.5; mean loss of smell VAS scores were 8.2 versus 9.5; and mean LMS were 14.9 versus 20.3, respectively. Olfactory function was evaluated in all five studies using the 16-SSIT, and the mean baseline value was 3.0. In contrast, in the SYNAPSE trial, the evaluation of olfactory function was performed using the UPSIT; however, only the mean variation at 52 weeks was reported, without providing baseline values. Conversely, an evaluation of the sense of smell was not conducted in the MERIT trial. Mean baseline scores are summarized in Table 1.

- Outcomes after 6 and 12 months of mepolizumab

In real-world studies, treatment with mepolizumab was associated with significant clinical and biochemical improvements in patients with CRSwNP. After 6 months of therapy, mean changes from baseline were observed in BEC (−546.1 cells/μL), SNOT-22 (−31.2), NPS (−2.0), 16-SSIT (+3.7), and loss of smell VAS (−2.7). Continued treatment for 12 months yielded further improvements, with mean changes of −639.6, −31.9, −2.9, +6.5, and −4.9, respectively. Finally, even LMS passed from 14.9 to 10.1 after one year. Mean values at 6 and 12 months, as well as mean variation and p-value, are displayed in Table 2.

Compared to the SYNAPSE cohort, patients in real-life studies achieved slightly greater improvements in SNOT-22, NPS, LMS, and sense of smell, despite methodological differences in the olfactory tests employed across phase III and phase IV studies. In the SYNAPSE trial, the mean changes from baseline were − 29.4 for SNOT-22, − 0.9 for NPS, + 1.7 for the University of Pennsylvania Smell Identification Test (UPSIT), and − 2.8 for the loss of smell VAS [6]. The data are shown as a forest plot in Fig. 2.

- Tolerability and response to treatment

AEs deemed related to mepolizumab treatment were reported in 55 out of 392 patients (14.0%) in real-world studies, with only 6 cases (1.5%) classified as severe. The most commonly reported EA was injection site reactions, occurring in 21 patients (38.2%), followed by musculoskeletal pain, including muscular and joint pain, reported in 10 patients (18.2%). Other frequently observed AEs included nasopharyngitis, pharyngodynia, and fatigue, each reported by 4 patients (7.3%). Severe AEs leading to treatment discontinuation included myalgia ($n=2$), a sarcoidosis-like reaction ($n=1$), herpes zoster reactivation ($n=1$), arthritis ($n=1$), and gastroenteritis ($n=1$). A total of 37 patients discontinued mepolizumab: 6 due to severe AEs and 31 due to inadequate treatment response (7.9%). Additionally, 4 patients were lost in follow-up.

Similarly, in the Phase III trials, the overall rate of treatment-related AEs was 11.2%, although none were classified as severe. Furthermore, 18 patients (6.3%) required rescue ESS during the 52-week study period as they were considered non-responders [6].

Discussion

Initially approved for the treatment of eosinophilic asthma, mepolizumab was subsequently incorporated into the therapeutic arsenal for managing severe and refractory type 2 CRSwNP, following the positive results demonstrated in the SYNAPSE randomized, double-blinded, phase III clinical trial [6]. Since its approval for routine clinical use, several real-life studies have reported encouraging results across laboratory, clinical, and radiological outcomes, as well as favorable tolerability and safety profiles [11–23]. However, a review comparing results obtained in phase III and phase IV studies is still lacking, as such comparisons are challenging due to differences in inclusion criteria and the use of different olfactory tests.

The demographic characteristics of patients, including sex and age, were comparable between phase III clinical trials and real-life studies. In both groups, neither age nor sex appeared to influence clinical outcomes. Interestingly, a higher proportion of patients with comorbid eosinophilic asthma (79.3% vs. 71.3%) and N-ERD (31.8% vs. 23.8%) was observed in the phase IV studies. This finding was not unexpected for various reasons. Firstly, mepolizumab was initially approved for eosinophilic asthma prior to its indication for CRSwNP. Secondly, the present review included four articles specifically targeting asthmatic patients with comorbid CRSwNP [16, 20–22]. However, even after excluding these studies, the prevalence of asthma in real-life cohorts remained high, with 368 out of 494 patients (74.5%) affected. This may indicate a tendency in routine clinical practice to preferentially prescribe mepolizumab for patients with CRSwNP and coexisting difficult-to-treat eosinophilic asthma, particularly those with recurrent

Table 1 Patients' demographic and anamnestic characteristics from phase IV and III studies

Author	Patients (*N*)	Age (mean±SD)	Asthma (*N*, %)	*N*-ERD (*N*, %)	Atopy (*N*, %)	Previous ESS (*N*,%)	Baseline BEC (mean±SD)	Baseline SNOT-22 (mean±SD)	Baseline NPS (mean±SD)	Baseline 16-SSIT (mean±SD)	Baseline LoS VAS (mean±SD)	Baseline LMS (mean±SD)
Dominguez - Sosa et al.*, [10]	55	53.7±NA	49 (89.1)	28 (50.9)	29 (52.7)	30 (54.5)	500±NA	76±NA	4±NA	NA	NA	NA
Cantone et al., [11]	45	59.7±NA	21 (46.7)	8 (17.8)	NA	42 (93.3)	421±302.7	61.3 ± 24.1	5.2 ± 2.2	4.1 ± 2.3	6.2 ± 3.9	NA
Orlando et al., [19]	27	57.7±NA	25 (92.6)	10 (37.0)	14 (51.9)	19 (70.4)	800.0±NA	58.6±NA	5.6±NA	5.0	9.6	12.8±NA
Ottaviano et al., [13]	90	61.0±NA	78 (86.7)	28 (31.1)	55 (61.1)	83 (92.2)	NA	55.0±NA	6.0±NA	3.0	9.0	NA
Cavaliere et al., [14]	20	63.7±NA	17 (85.0)	NA	11 (55.0)	17 (85.0)	580±420	48.3 ± 13.2	5.1 ± 1.05	NA	8.5 ± 1.31	NA
Galletti et al.*, [15]	29	54.0±NA	18 (62.1)	11 (37.9)	22 (75.9)	25 (86.2)	NA	NA	NA	NA	NA	NA
Gallo et al., [20]	45	52.2±10.9	45 (100.0)	NA	15 (33.3)	32 (71.1)	804.7±461.5	54.8±25.9	3.0±NA	NA	NA	NA
Detoraki et al., [16]	44	44.0±NA	44 (100.0)	10 (22.7)	NA	39 (88.6)	863±900	51.6±21.2	2.8±3.07	NA	NA	NA
Galletti et al.*, [17]	67	55.0±NA	43 (64.2)	23 (34.3)	48 (71.6)	55 (82.1)	NA	64±NA	6±NA	2	NA	NA
Moffa et al., [18]	17	57.6±16.99	9 (52.9)	2 (11.8)	11 (64.7)	16 (94.1)	592±460	50.7±23.32	5.2±0.79	NA	7.5±3.11	NA
Demir et al.*, [21]	14	43.5±NA	14 (100.0)	8 (57.1)	6 (42.9)	NA	1175	NA	4±NA	NA	NA	19±NA
Viskens et al., [12]	144	53.0±13	108 (75.0)	38 (26.4)	85 (59.0)	143 (99.3)	500±300	51.0±NA	4.1±NA	NA	8.2	NA
Kurosawa et al., [22]	11	55.0±NA	11 (100.0)	6 (54.5)	2 (18.2)	NA	409.8±NA	57.6±NA	4.7±NA	NA	NA	NA
Overall	**608**	**53.7±5.50**	**482 (79.3%)**	**187 (31.8%)**	**283 (59.7%)**	**501 (83.9%)**	**462.7±238.6**	**57.6±8.60**	**4.7±1.32**	**3.0±0.5**	**8.2±1.2**	**14.9±3.05**
SYNAPSE	206	48.6±13.6	140 (68.0)	45 (21.8)	NA	206 (100.0)	390±0.88	63.7	5.4	NA	9.6	NA
MERIT	80	53.0±10.7	64 (80.0)	23 (28.8)	NA	52 (65.0)	400±0.641	56.9±18.94	5.9±1.27	NA	9.4±1.21	20.3±3.25
Overall	286	49.3±12.94	204 (71.3%)	68 (23.8%)	NA	258 (90.2%)	392.8±0.826	61.8	5.5	NA	9.5	NA

Table 2 Mean sinonasal scores at baseline and after 6 and/or 12 months from phase IV and III studies

Author	BEC 6 months (mean ± SD)	ΔBEC6 months(p-value)	SNOT226 months (mean ± SD)	ΔSNOT22 6 months (p-value)	NPS 6 months (mean ± SD)	ΔNP6 6 months (p-value)	LoS VAS 6 months (mean ± SD)	ΔLoS VAS 6 months (p-value)	16SSIT 6 months (mean ± SD)	Δ16SSIT 6 months (p-value)	BEC12 months (mean ± SD)
Dominguez - Sosa et al.* [10]	97 ± NA	-403 (<0.001)	10 ± NA	-63 (<0.001)	1 ± NA	-3 (<0.001)	NA	NA	NA	NA	NA
Cantone et al. [11]	75 ± 71.4	-346 (0.001)	19.5 ± 8.4	-41.8 (0.001)	2.5 ± 1.4	-2.7 (0.004)	NA	NA	7.5 ± 2.8	+3.4(0.02)	NA
Orlando et al. [19]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	85.2 ± NA
Ottaviano et al. [13]	NA	-960 (<0.001)	28.4 ± NA	-26.6 (<0.001)	4.3 ± NA	-1.7 (<0.001)	7.5 ± NA	-1.5 (<0.001)	4.2 ± NA	+1.2 (<0.001)	NA
Cavaliere et al. [14]	120 ± 49	-460 (<0.001)	31.9 ± 12.37	-16.4 (<0.001)	3.7 ± 1.04	-1.4 (<0.001)	4.1 ± 2.59	-4.4 (<0.001)	NA	NA	90 ± NA
Galletti et al.* [15]	400 ± NA	-400 (0.001)	32.0 ± NA	-33 (<0.001)	4.0 ± NA	-2 (<0.001)	NA	NA	7.0 ± NA	+5 (<0.001)	500
Gallo et al. [20]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	107.5 ± 104.6
Detoraki et al. [16]	102.2 ± 106.7	-760.8 (<0.001)	31.7 ± 17.36	-32.3(<0.001)	1.7 ± 2.37	-1.1(0.0024)	NA	NA	NA	NA	73.7 ± 72.9
Galletti et al.* [17]	NA	NA	35 ± NA	-29 (<0.001)	5 ± NA	-1 (<0.001)	NA	NA	6 ± NA	+4 (<0.001)	NA
Moffa et al. [18]	108 ± 90	-574(0.0049)	25.1 ± 15.62	-25.6(0.00002)	3.6 ± 0.87	-1.6 (0.00034)	4.8 ± 2.81	-2.7(0.064)	NA	NA	78.5 ± 50
Demir et al.* [21]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Viskens et al. [12]	NA	NA	32.1 ± NA	-18.9 (<0.0001)	1.9 ± NA	-2.2 (<0.0001)	5.5 ± NA	-2.7(<0.0001)	NA	NA	NA
Kurosawa et al. [22]	55.7 ± NA	-354	NA	NA	NA	NA	NA	NA	NA	NA	49.5 ± NA
Overall	**160.0 ±114.4**	**-546.1(0.0003)**	**25.7 ±13.65**	**-31.2(0.0053)**	**3.3 ± 2.08**	**-2.0(0.222)**	**5.7±1.47**	**-2.7(<0.05)**	**3.0 ± 1.42**	**+3.7(0.018)**	**295.0 ±159.5**
SYNAPSE [6]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MERIT [7]	NA	NA	Na	NA	NA	NA	NA	NA	NA	NA	NA
Overall	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**

Author	ΔBEC 12 months (p-value)	SNOT22 12 months (mean ± SD)	ΔSNOT22 12 months (p-value)	NPS 12 months (mean ± SD)	ΔNPS 12 months (p-value)	16-SSIT 12 months (mean ± SD)	Δ16SSIT 12 months (p-value)	LoS VAS 12 months (mean ± SD)	ΔLoS VAS 12 months (p-value)	LMS12 months (mean ± SD)	ΔLMS12 months
Dominguez - Sosa et al.* [10]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cantone et al. [11]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Orlando et al. [19]	-714.8(<0.001)	25.7 ± NA	-32.9 (<0.005)	3.0 ± NA	-2.6 (<0.001)	9.6 ± NA	+4.6 (<0.001)	5.2 ± NA	-4.4(<0.001)	6.5 ± NA	-6.3 (<0.05)
Ottaviano et al. [13]	-1020(<0.001)	23.1 ± NA	-31.9 (<0.001)	3.6 ± NA	-2.4 (<0.001)	6.6 ± NA	+3.6 (<0.001)	7.2 ± NA	-1.8 (<0.001)	NA	NA

Table 2 (continued)

Author	ΔBEC 12 months (p-value)	SNOT22 12 months (mean ± SD)	ΔSNOT22 12 months (p-value)	NPS 12 months (mean ± SD)	ΔNPS 12 months (p-value)	16-SSIT 12 months (mean ± SD)	Δ16SSIT 12 months (p-value)	LoS VAS 12 months (mean ± SD)	ΔLoS VAS 12 months (p-value)	LMS12 months (mean ± SD)	ΔLMS12 months
Cavaliere et al. [14]	-490 (<0.001)	16.6 ± 8.49	-31.7 (<0.001)	1.9 ± 1.73	-3.2 (<0.001)	NA	NA	2.7 ± 1.38	-5.8 (<0.001)	NA	NA
Galletti et al.* [15]	-300 (0.002)	22 ± NA	-43 (<0.001)	3 ± NA	-1 (<0.001)	11 ± NA	+9 (<0.001)	NA	NA	NA	NA
Gallo et al. [20]	-697.2 (<0.001)	31.5 ± 21.3	-23.3 (<0.001)	2.0 ± NA	-1 (<0.001)	NA	NA	NA	NA	NA	NA
Detoraki et al. [16]	-789.3 (<0.001)	29.7 ± 21.5	(<0.001)	1.8 ± 2.56	-1(0.99)	NA	NA	NA	NA	NA	NA
Galletti et al.* [17]	NA	25 ± NA	-39 (<0.001)	4 ± NA	-2 (<0.001)	9 ± NA	+7 (<0.001)	NA	NA	NA	NA
Moffa et al. [18]	-513.5(0.25)	20.3 ± 15.06	-30.4 (0.0026)	2.6 ± 0.79	-2.6(0.018)	NA	NA	-4.7 ± 2.63	-2.8(0188)	NA	NA
Demir et al.* [21]	NA	NA	-45(<0.001)	4 ± NA	0(0.335)	NA	NA	NA	NA	17 ± NA	-2(0.432)
Viskens et al. [12]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kurosawa et al. [22]	-360.3	NA	-18	NA	NA	NA	NA	NA	NA	NA	-3
Overall	**-639.6(0.000003)**	**23.5 ± 2.12**	**-31.9(0.003)**	**2.9 ± 0.84**	**-2.9(0.041)**	**9.2 ± 1.41**	**+6.5(0.0029)**	**4.9 ± 1.85**	**-3.9(<0.05)**	**10.1 ± NA**	**-4.44(<0.05)**
SYNAPSE [6]	NA	34.3	-29.4(0.0032)	4.5	-0.9 (<0.0001)	NA	+1.7(0.3)	NA	-2.8(0.02)	NA	NA
MERIT [7]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Overall	**NA**	**34.3**	**-29.4(0.0032)**	**4.5**	**-0.9 (<0.0001)**	**NA**	**NA**	**NA**	**-2.8(0.02)**	**NA**	**NA**

BEC blood eosinophil count *SNOT-22*, sinonasal outcomes test-22, *16-SSIT* 16-item sniffin sticks test, *NPS* nasal polyps score, *VAS* visual analogue scale, *LMS* Lund-Mackay score, * median value, not mean

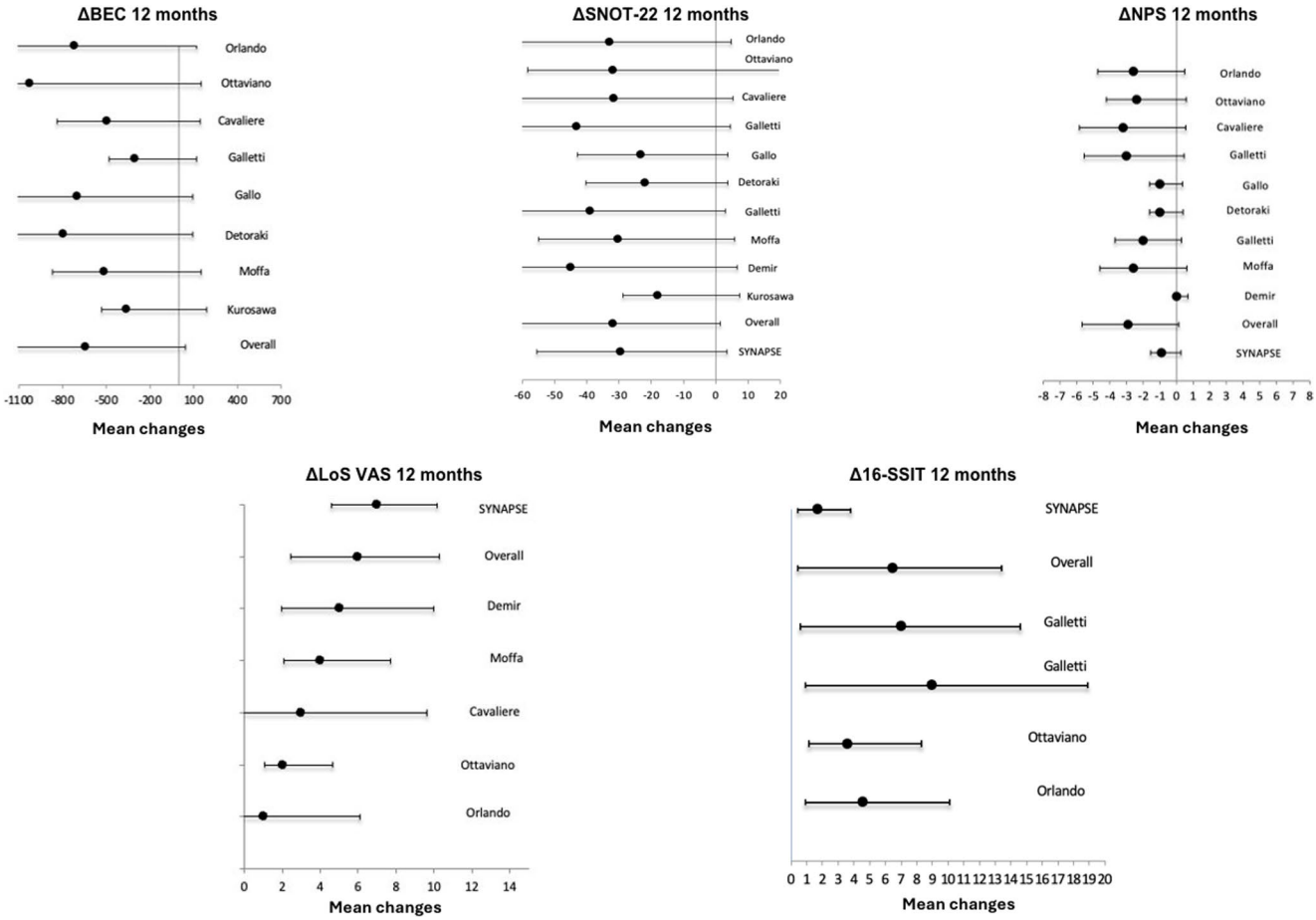

Fig. 2 Forest Plot comparison between real-life studies and SYNAPSE clinical trial after 12 months of mepolizumab. BEC: blood eosinophil count; SNOT-22: sinonasal outcomes test-22; 16-SSIT: 16-item sniffin sticks test; NPS: nasal polyps score; VAS: visual analogue scale

exacerbations within the preceding 12 months [23]. This trend may be at least partially supported by the markedly higher baseline BEC observed in real-life studies compared with those reported by SYNAPSE and MERIT trials, further suggesting the use of mepolizumab in patients with a presumed greater burden of eosinophilic inflammation. Moreover, the tendency to initiate anti–IL-5 therapy in CRSwNP patients with elevated baseline BEC may also reflect a precautionary approach, aiming to prevent peripheral blood hypereosinophilia and related adverse events previously reported in patients receiving dupilumab [24, 25]. Notably, neither phase III nor phase IV studies highlighted significant differences in treatment outcomes when comparing patients with and without comorbid eosinophilic asthma. On the contrary, patients with comorbid N-ERD exhibited more variable responses. Dominguez-Sosa et al. reported a greater improvement in NPS and BEC in N-ERD patients, whereas Ottaviano et al. and Orlando et al. observed less favorable outcomes in terms of SNOT-22 and 16-SSIT after one year of treatment, respectively [10, 13, 19].

With regard to prior surgery, a higher rate of post-ESS patients was observed in phase III cohorts compared with phase IV cohorts (90.2% vs. 83.9%), which was expected, as a history of prior surgery was an explicit inclusion criterion in the SYNAPSE trial [6]. However, no significant differences in outcomes were observed when comparing surgically naive and post-ESS patients treated with mepolizumab, although the small number of surgically naïve patients does not permit firm conclusions to be drawn.

When considering the entire cohort, regardless of type-2 comorbidities and previous surgery, improvements in rhinology-specific outcomes have been reported as early as 1 month after initiating IL-5 therapy, with positive trends persisting at 6 and 12 months [10–18]. Measures, including SNOT-22, NPS, LMS, and sense of smell, exceeded improvements reported in the SYNAPSE trial, despite comparable baseline characteristics. Notably, in real-life studies, the sense of smell was assessed using a 16-item identification test, whereas the SYNAPSE trial employed the 40-item UPSIT. While the 40-item UPSIT may theoretically

detect more subtle changes in olfactory performance due to its greater sensitivity and item range, the real-life cohort showed a notably greater mean improvement in olfactory function after 1 year (+ 6.5 points) than the SYNAPSE cohort (+ 1.7 points). Unfortunately, data about the effective prevalence of anosmic, hyposmic, and normosmic patients is lacking in both phase III trials. In fact, olfactory impairment was not even considered an eligibility criterion. In detail, the MERIT trial did not provide any information on sense of smell, whereas the SYNAPSE trial reported only the mean UPSIT change over time. The absence of data on the proportion of baseline distribution of olfactory function prevents a clear understanding of how the observed mean gain was distributed across individuals. Indeed, this improvement could reflect heterogeneous response patterns, such as many patients experiencing modest improvements with few non-responders, or conversely, a smaller subset achieving substantial gains while others remained stable or worsened. Among real-life studies, only two studies reported the effective proportion of anosmic patients before and after mepolizumab. In particular, Dominguez-Sosa et al. and Orlando et al. reported a marked decrease of anosmic patients from 53 (94.5%) to 14 (25.5%) after 6 months and from 81.5% to 44.4% after 12 months, respectively [10, 20]. In conclusion, the discrepancy in mean sense of smell variation suggests that factors beyond test sensitivity (such as differences in patient population, treatment adherence, or real-world conditions) may play a significant role in observed outcomes.

Finally, mepolizumab was proven to be safe even in the real-life context. AEs potentially associated with anti-IL-5 therapy were reported by 55 out of 392 patients from real-world studies (14.0%). Of these, only six events (1.5%) were considered severe and led to treatment discontinuation. These included two cases of myalgia, one case of sarcoidosis-like reaction, one case of herpes zoster reactivation, one case of arthritis, and one case of gastroenteritis [12, 17, 20]. Interestingly, phase IV trials reported a slightly lower incidence of treatment-related AEs (11.2%), and no patients discontinued treatment due to severe AEs [6, 7]. On the other hand, a slightly greater proportion of SYNAPSE patients discontinued mepolizumab requiring rescue ESS during the 52-week trial due to poor or absent response to treatment compared to real-life studies (8.7% vs. 8.0%). This difference, though small, may suggest that patient selection in real-world settings is more precise, possibly reflecting better alignment of treatment indications with individual disease phenotypes. However, the margin is too narrow to draw definitive conclusions. Certainly, mepolizumab has been demonstrated to reduce the use of rescue SCS and ESS, which may be partly due to its ability to decrease nasal polyps tissue eosinophils [26, 27].

As with all real-life reviews, this study has several limitations that may impact the accurate representation of mepolizumab's effects in real-world settings. The primary limitation is the relatively small number of included studies and enrolled patients, which may reduce the generalizability of our findings. Additionally, variability among ENT departments in the methods used to assess olfactory function, as well as inconsistencies in the reporting of demographic and outcome data, posed challenges for direct comparisons in the real-world setting. Moreover, the comparison between phase III and phase IV studies may be further complicated by differences in demographic (e.g., atopy), clinical (e.g., 16-SSIT), and statistical (e.g., least squares mean) methods.

Future research is expected to include a larger number of surgically naïve patients, as the updated EPOS/EUFOREA guidelines have expanded the indication for monoclonal antibody therapy to individuals unfit for surgery [9]. Studies with larger cohorts and longer follow-up periods will be essential to achieve a deeper understanding of mepolizumab's effectiveness in CRSwNP and to better define its role within the ENT therapeutic armamentarium for severe and recalcitrant disease.

Conclusion

To the best of our knowledge, this is the first narrative review summarizing the results of phase IV studies on the safety and efficacy of mepolizumab in a real-life context and comparing them to findings reported by phase IV clinical trials. Mepolizumab has been demonstrated to be effective in reducing the burden of CRSwNP, even if it was not possible to identify any laboratory or anamnestic prognostic factor able to predict response to the treatment with the anti-IL5. However, a greater prevalence of non-responder patients has been reported in the real-life studies compared to phase III trials, probably due to the higher BEC and disease severity. Future studies are warranted to establish universally accepted prescription and response criteria, as well as a more adequate strategy in the case of non-responder patients.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and informed consent As it is a review of the literature, approval of the ethical committee and informed consent were not necessary.

Competing interests Authors disclose financial and non-financial interests.

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