Review Article

Improving patient outcomes: Mepolizumab's impact in IL-5-mediated diseases

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ABSTRACT

The Interleukin-5 (IL-5)-mediated pathogenic role of eosinophils in airway disorders including severe eosinophilic asthma (SEA), chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic granulomatosis with polyangiitis (EGPA), and rare hyper-eosinophilic syndrome (HES) is well established. Mepolizumab, an IL-5-targeting humanised antibody, is approved as an add-on maintenance therapy for SEA, EGPA, CRSwNP, and HES. Here, we review the safety and efficacy findings of mepolizumab in clinical trials and real-world evidence studies in patients with SEA, CRSwNP, EGPA, and HES. We specifically explore the data on mepolizumab that support early initiation of IL-5-targeted therapy to maximise its corticosteroid-sparing effect. This review consolidates the clinical data on mepolizumab, highlights other promising IL-5-targeting agents, and supports the IL-5 pathway as the key therapeutic target across eosinophilic indications.

KEY WORDS: CRSwNP, EGPA, eosinophilic asthma, hyper-eosinophilic syndrome hyper-eosinophilia, IL-5, mepolizumab, NUCALA

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INTRODUCTION

Interleukin (IL-5) is a homo-dimeric cytokine that promotes the survival, differentiation, activation, growth, and chemotaxis of eosinophils. The pathogenic role of eosinophils in type-2 inflammation mediated via IL-5 in airway inflammatory diseases including severe eosinophilic asthma (SEA, more recently referred to as severe asthma-eosinophilic phenotype), chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic granulomatosis with polyangiitis (EGPA),[1-4] and rare hyper-eosinophilic syndrome (HES)[5] has been well documented. As a result, several anti-IL-5 therapies have been proposed and some have already been approved to treat these conditions.[6] Traditional therapies to treat these diseases included corticosteroids (CS, either oral or intra-nasal) and immunosuppressants.[7] However, severe cases of eosinophilic asthma can be resistant to oral CS, leading to inadequate symptom control, frequent exacerbations, and uncontrolled eosinophilia, resulting in comorbid CRSwNP or EGPA wherein IL-5 is one of the leading cytokines beyond the eosinophils.[8] The promising biologics that target IL-5 or its receptor (IL-5R) include

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mepolizumab and reslizumab[9] (targeting IL-5), and benralizumab[10] (targets IL-5Rα chain, induces antibody dependent cellular cytotoxicity).

Mepolizumab (SB-240563, Nucala™, GSK), a humanised immunoglobulin G1 antibody, is a first-in-class IL-5-targeting antibody, which has been approved in several countries by their respective regulatory authorities and by the United States (US) Food and Drug Administration (FDA) as an add-on maintenance therapy for eosinophilic disorders including SEA,[11] EGPA,[12] CRSwNP,[13] and HES.[14] For HES, mepolizumab is the only currently approved biologic treatment, while for relapsing-remitting or refractory EGPA, it has been recommended as first-line treatment. Mepolizumab is the only biologic that has received approval for use as an add-on/maintenance therapy across all four of these eosinophilic disorders, whereas other biologics like benralizumab[10] and reslizumab[9] are approved only for SEA; however, benralizumab is also being assessed as a plausible treatment option in EGPA (NCT04157348).[15]

Over 30 completed clinical trials and several real-world evidence (RWE) studies have documented the safety and efficacy of mepolizumab in four approved indications [Figure 1]. Based on literature, this review aims to: 1) consolidate the safety and efficacy findings reported in clinical trials and various RWE studies of mepolizumab across four indications, to aid the patients and physicians in making informed treatment choices, 2) suggest if IL-5 targeting can be the mechanism of choice across eosinophilic indications based on the success of mepolizumab and other such biologics to treat these conditions, and 3) understand if the early initiation of the targeted biologic therapies can be helpful in the management of eosinophilic conditions.

REGULATORY APPROVALS OF MEPOLIZUMAB FOR EOSINOPHILIC DISORDERS

Based on the clinical trials evidence, mepolizumab [100 mg every 4 weeks (Q4W) subcutaneous (SC) dose] was first approved by the US FDA in 2015 for patients (≥12 years) with eosinophilic phenotype-SEA, and the approval was further extended in 2019 to children aged between 6 and 11 years (40 mg Q4W SC dose).[13,16] In 2017, mepolizumab (300 mg Q4W SC dose) was approved for patients with EGPA aged ≥18 years, and in 2020 for patients with HES (≥6 months without an identifiable non-hematologic secondary cause) aged ≥12 years. Recently, in 2021, mepolizumab (100 mg Q4W SC dose) received approval for CRSwNP for patients aged ≥18 years [Figure 2]. Currently, mepolizumab has been approved in the US, Europe, and over 20 other countries for SEA and EGPA. For HES, it is approved in the US, Brazil, and Argentina.

EFFICACY AND SAFETY OF MEPOLIZUMAB

Severe eosinophilic asthma (SEA)

Overall, 5% to 10% of all asthma patients present a more severe form of the disease, atopic asthma, and about 50% of these patients with atopic asthma are further characterised by eosinophilia leading to SEA.[17] Patients with SEA may require daily maintenance oral CS to reduce exacerbation risk or to control day-to-day symptoms.[18] Thus, biologics

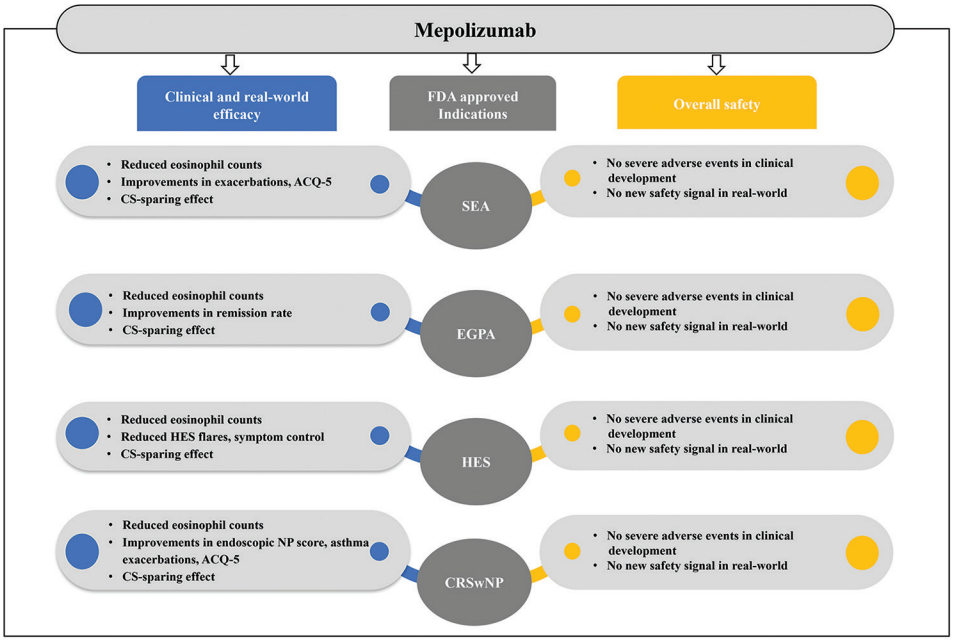

Figure 1: Efficacy and safety of mepolizumab in the clinical and real worlds. ACQ-5, asthma control questionnaire-5; CS, corticosteroid; CRSwNP, chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis; FDA, Food and Drug Administration; HES, hyper-eosinophilic syndrome; NP, nasal polyp; SEA, severe eosinophilic asthma

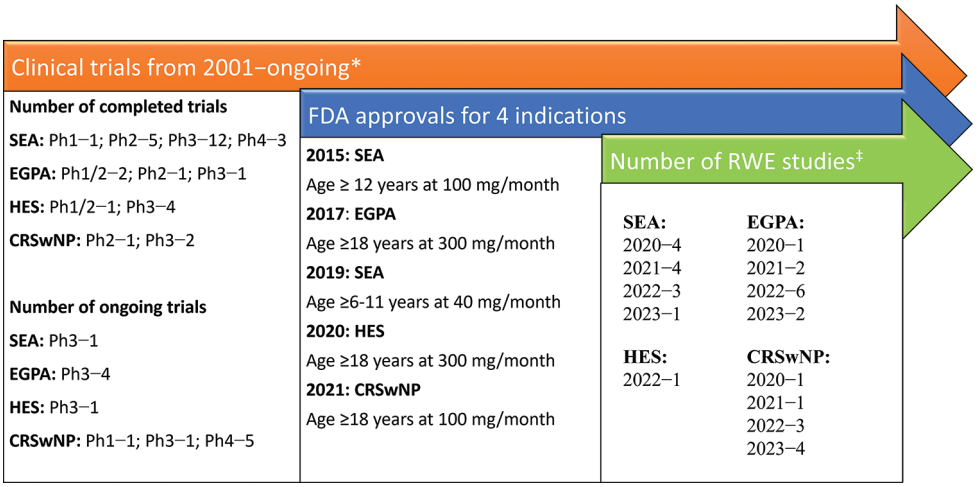

Figure 2: Journey of mepolizumab from clinical development to real-world use. *As extracted from clinicaltrial.gov on 08 Aug 2023, not-active, not-recruiting, withdrawn studies are not included. ‡Records extracted from PuBMed with keywords RWE/observational/retrospective; mepolizumab and further selected based on relevance. CRSwNP, chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis; FDA, Food and Drug Administration; HES, hyper-eosinophilic syndrome; Ph, phase; SEA, severe eosinophilic asthma; RWE, real-world evidence

such as mepolizumab are recommended as a plausible option for a personalized treatment approach in patients with SEA. A substantial number of clinical and real-world studies [Table 1] have assessed the efficacy and safety of mepolizumab in patients with SEA and have demonstrated improved clinical outcomes with manageable safety profiles.[19-21]

Clinical development and efficacy

Although the early studies of mepolizumab in asthma failed to show significant clinical improvements,[22,23] an observed numerical decrease in exacerbations in patients with severe asthma triggered investigation of mepolizumab in SEA. In the first landmark study, MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma), both intravenous (IV) and SC mepolizumab significantly reduced the rate of exacerbations ($P < 0.001$) and associated emergency department visits or hospitalisation versus placebo.[24] Mepolizumab also demonstrated benefits in SEA patients treated with inhaled CS plus controllers such as long-acting beta-2 agonist.[25] Similar reduction in the rate of exacerbations and improvements in asthma symptoms were reported in the DREAM (Dose Ranging Efficacy and Safety with Mepolizumab) study,[26] in a long-term DREAM extension COLUMBA (Open-label Long-Term Extension Safety Study of Mepolizumab in Asthmatic Subjects) study,[19] the MUPPITS-2 (study in children and adolescents aged 6 to 17 years),[27] and COMET study.[28]

The MUSCA study showed significant improvements in health-related quality-of-life (HRQoL) of patients with SEA.[29] SIRIUS (Steroid Reduction with Mepolizumab Study) reported reduced use of maintenance oral glucocorticoids and a significant reduction ($P = 0.007$) in the glucocorticoid dose (50%) in patients with SEA receiving adjunctive SC mepolizumab.[30] A *post hoc* analysis of the MENSA and MUSCA studies demonstrated significant improvements in the morning peak expiratory flow (nocturnal asthma exacerbations),[31] improvements in HRQoL, and exacerbations with mepolizumab treatment regardless of the presence of nasal polyposis.[32] Furthermore, mepolizumab was shown to reduce the number of blood and sputum eosinophils, which allows prednisone sparing in patients with asthma and sputum eosinophilia.[33]

The OSMO (Omalizumab Switch to MepOlizumab) study showed a reduction in the annualized rate of clinically significant exacerbations in patients with SEA who were switched from omalizumab to mepolizumab.[34]

Real-world evidence of efficacy

The efficacy of mepolizumab in SEA patients has been demonstrated in multiple RWE studies. In the prospective REALITI-A study, patients with severe asthma reported reduction in the median maintenance oral CS and exacerbations ($P < 0.001$) at 1 year after treatment. Additionally, 64% of patients had a dose reduction of ≥50% versus baseline and 43% of patients discontinued maintenance oral CS.[35] Other RWE studies advocate the use of mepolizumab to reduce the significant and long-standing disease burden of SEA[21,36] and to improve asthma control along with the CS-sparing effect in patients with SEA.[37] In a Finnish retrospective, non-interventional RWE study[38] and a 5-year Spanish RWE study, mepolizumab could sustain long-term efficacy, with increased asthma control, reduction in the exacerbation rate, and improvement in lung function.[39] In another RWE study, about 84% of patients were classified as responsive to mepolizumab regardless of the comorbidities or other characteristics (sex, body mass index, age, smoking).[40] Effectiveness of mepolizumab was further corroborated by other RWE reports.[41-45] *Post hoc* RWE analysis of the COSMOS study revealed that the cessation of mepolizumab is associated with a rise in the blood eosinophil count and

Table 1: Clinical trial and RWE data with mepolizumab in SEA

Study	Patients and Intervention	Primary endpoint	Key secondary outcomes
Randomized clinical trials and *post hoc* studies			
MENSA (Ortega *et al*., 2014)	*n*=191, PBO; *n*=191, 75 mg mepo IV; *n*=194, 100 mg mepo SC Q4W for 32 weeks	Rate of exacerbations (difference from PBO) • Mepo IV: reduced by 47% (95% CI, 29–61) • Mepo SC: reduced by 53% (95% CI, 37–65) • *P*<0.001 for both	• Exacerbations necessitating an emergency department visit or hospitalization reduced by 32% vs 61% in IV vs SC group, respectively, vs PBO • Significant improvement in pre- and postbronchodilator FEV_1 in both IV and SC groups vs PBO (*P*<0.05) • SGRQ score was 6.4 points and 7.0 points greater in the IV and SC groups vs PBO (*P*<0.001) • Improvement in the ACQ-5 score was 0.42 points and 0.44 points greater in the IV and SC group, respectively, vs PBO (*P*<0.001) • AEs were similar in three groups (84% in IV, 78% in SC and 83% in PBO)
Post-hoc analysis, MENSA (Shimoda *et al*., 2017)	Japanese subgroup *n*=50, 75 mg mepo IV; *n*=194, 100 mg mepo SC Q4W for 32 weeks	Rate of exacerbations (difference from PBO) • Mepo IV: reduced by 90% (RR: 0.10; 95% CI, 0.02–0.57; *P*=0.010) • Mepo SC: reduced by 62% (RR: 0.38; 95% CI, 0.12 to 1.18; *P*=0.094)	• No exacerbations requiring emergency department visit/ hospitalization were reported in IV group • Exacerbations were reduced by 73% (RR: 0.27; 95% CI, 0.06 to 1.29; *P*=0.102) in SC group • Mepo IV and SC treatment decreased SGRQ scores at week 32 by 9.5 (*P*=0.083) and 7.9 (*P*=0.171) points more than PBO
DREAM (Pavord *et al*., 2012)	*n*=159, PBO; *n*=154, 75 mg mepo; *n*=152, 250 mg mepo, and *n*=156, 750 mg mepo IV Q4W for 52 weeks	Rate of clinically significant exacerbations: PBO 2.40/patient/year • Mepo 75 mg 1.24/patient/year (48% reduction, 95% CI, 31 to 61%; P<0.0001) • Mepo 250 mg 1.46/patient/ year (39% reduction, 19−54%; *P*=0.0005) • Mepo 750 mg 1.15/patient/ year (52% reduction, 36−64%; *P*<0.0001)	• Rate of exacerbations requiring admission were 0.18 (0.29), 0.11 (0.35), 0.12 (0.32) and 0.07 (0.39) in PBO, 75 mg, 250 mg and 750 mg group, respectively • No statistically significant between-group differences in prebronchodilator FEV1 at week 52 • Change in score on asthma QoL questionnaire was 0.71 (0.09), 0.80 (0.09), 0.77 (0.09) and 0.93 (0.09) in PBO, 75 mg, 250 mg and 750 mg group, respectively
COLUMBA (Khatri *et al*., 2019)	*n*=347, 100 mg mepo SC Q4W until a protocol-defined stopping criterion was met	Frequency of AEs • 326 patients (94%) reported AE; 97 (28%) reported AE related to study treatment • Respiratory tract infection (*n*=231 [67%]), headache (*n*=99 [29%]), asthma worsening (*n*=94 [27%]), and bronchitis (*n*=73 [21%]) were the most reported on-treatment AEs	• Annualized rate of on-treatment exacerbations was 0.68 events/y (95% CI, 0.60–0.78 events/y), 61% reduction from the off-treatment period between DREAM and COLUMBA • Prebronchodilator FEV1 increased by week 24, but returned to baseline level afterwards • Mean reduction from baseline in ACQ-5 score of 0.47 points
MUPPITS-2 (Study in children aged 6-17 years) (Jackson *et al*., 2022)	*n*=146, mepo; *n*=144, PBO; 6-11 years: 40 mg 12-17 years: 100 mg Q4W SC for 52 weeks	• The annualized rate of asthma exacerbations was 0.96 (95% CI, 0.78−1.17) with mepo and 1.30 (95% CI, 1.08−1.57) with PBO (RR: 0.73; 95% CI, 0.56−0.96; *P*=0.027)	• Mepo significantly reduced blood eosinophil counts, (−299 [95% CI, −363, −235], *P*<0.0001) • No statistically significant between-group differences in FEV1% predicted, FEV1/FVC or measures of impulse oscillometry
COMET (Moore *et al*., 2022)	*n*=151, PBO and *n*=144, mepo 100 mg Q4W SC for 52 weeks	Time to first clinically significant exacerbation • 61% increase in risk for patients who stopped vs continued mepo • HR=1.61 (95% CI, 1.17–2.22; *P*=0.004)	• Stopping vs continuing mepo led to a decrease in asthma control (HR 1.52, 95% CI, 1.13–2.02; *P*=0.005) • Stopping vs continuing mepo led to a higher blood eosinophil count at week 52 (270 vs 40 cells·μL^{-1}); ratio 6.19, 95% CI, 4.89–7.83; *P*<0.001 • Stopping vs continuing mepo led to a non-significant trend for more pronounced worsening in lung function (prebronchodilator FEV1) by week 52 (*P*=0.186) • By week 52, the difference (95% CI) in ACQ-5 scores for patients stopping vs continuing mepo was 0.23 (−0.02–0.48; *P*=0.067)
COSMEX (COSMOS Extension) (Khurana *et al*., 2019)	*n*=340, mepo 100 mg Q4W SC for up to 172 weeks	Frequency of AEs • 315 patients (93%) reported AE; 51 (15%) reported treatment-related AE • 84 patients (25%) reported SAE; 3 (0.9%) reported treatment-related SAE	• Annualized on-treatment exacerbation rate: 0.93 (95% CI, 0.81−1.06) event/year • Annualized rate of on-treatment exacerbations requiring hospitalization, or an emergency department visit: 0.13 (95% CI, 0.10−0.18) event/year and 0.07 (95% CI, 0.05−0.10) event/year for those requiring hospitalization

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Table 1: Contd...

Study	Patients and Intervention	Primary endpoint	Key secondary outcomes
		Randomized clinical trials and *post hoc* studies	
MUSCA (Chupp *et al*., 2017)	*n*=277 PBO; *n*=274, mepo 100 mg Q4W SC for 24 weeks	Mean change from baseline in SGRO at week 24 • Mepo: -15.6 (SD=1.0) • PBO: -7.9 (SD=1.0) • Difference: -7.7 (95% CI, -10.5 to -4.9; *P*<0.0001)	• Treatment difference in pre-bronchodilator FEV1 at week 24: 120 (95% CI, 47–192; *P*=0.001) • 192 (70%) in mepo and 207 (74%) of in PBO reported at least one on-treatment AE
MAPLE (Yang *et al*., 2022)	Patients treated previously with mepo, prednisolone (0.5 mg/kg/d) followed by a 4 week washout period and then matched PBO or vice versa (*n*=27)	Change in asthma symptoms, QoL, lung function	• Prednisolone did not improve ACQ (change for prednisolone vs PBO, -0.23; 95% CI, -0.58–0.11), mini-Asthma QoL Questionnaire (0.03; 95% CI, -0.26–0.42), SGRQ, (0.24; 95% CI, -3.20–3.69), VAS scores for overall asthma symptoms (0.11; 95% CI, -0.58–0.80) • Trend towards improvement in FEV1
SIRIUS (Bel *et al*., 2014)	*n*=66 PBO; *n*=69, mepo 100 mg Q4W SC for 20 weeks	Degree of reduction in glucocorticoid use • Median dose reduction was 50% in mepo group, vs no reduction with PBO (*P*=0.007)	• 32% reduction in the annualized rate of exacerbations (1.44 vs 2.12, *P*=0.04) in mepo group (on reduced dose) vs PBO • Reduction of 0.52 points with respect to asthma symptoms (*P*=0.004)
		RWE studies	
REDES (Domingo Ribas *et al*., 2021)	*n*=318, Spanish patients Mepo 100 mg Q4W SC	Rate of clinically significant exacerbations: • Decreased by 77.5% • 50.6% of patients did not suffer any exacerbations during the 12 months of treatment	• Difference in FEV1 pre- and post-bronchodilator after starting mepo was 0.21 (0.46, 95% CI, 0.14–0.27) (*P*<0.001) • ACT increased by mean (SD) of 6.7±1.9 points at 12 months
REALITI-A (Pilette *et al*., 2020)	*n*=822 (Europe, Canada, and the United States) Mepo 100 mg Q4W SC	[primary endpoint not specified]	• Rates of clinically significant exacerbations decreased between pretreatment and posttreatment (rate ratio [95% CI] 0.29 [0.26−0.32]; *P*<0.001) • Median oral CS maintenance dose reduced by 75% at 1 year after treatment • 64% of patients had a reduction in maintenance oral CS dose of ≥50% vs baseline and 43% discontinued maintenance oral CS
Australian Mepo Registry (AMR) (Harvey *et al*., 2020)	*n*=309 Australian patients Mepo 100 mg Q4W SC	[primary endpoint not specified]	• Blood eosinophil levels reduction from median (IQR) 590 (400–830) cells·μL^{-1} at baseline to 100 (40–100) cells·μL^{-1} (*P*<0.001) at 3-month • Significant reductions in ACQ-5, median (IQR) 3.4 (3.0–4.2) at baseline versus 1.6 (0.8–2.6) at the 3-month (*P*<0.001) • Rate of exacerbation (per person-year) requiring oral CS reduced by 66% (95% CI, 59–71), *P*<0.001 • Need for hospitalization reduced by 54% (95% CI, 37–67; *P*<0.001) • Significant reduction in emergency room visits by 56% (95% CI, 25–74; *P*=0.003)
Finland, (Koistinen *et al*., 2022)	*n*=51 Finnish patients Mepo 100 mg Q4W SC	Changes from baseline in blood eosinophil count, FeNO, FEV1 *z*-score, AQLQ score and ACT score • Mean blood eosinophil count reduced by 84% (*P*<0.001) • Mean FeNO reduced by 26% (*P*=0.047) • FEV1 *z*-score improved by 14% (*P*=0.003) • AQLQ scores increased by 36% (*P*=0.06)	• Mean number of exacerbations per patient-year decreased by 82%, from 2.78/year during the baseline period to 0.51/year during the first-year follow-up (*P*<0.001) • Proportion of patients using oral CS decreased from 90% at baseline to 82% and 67% at 12 and 24 months, respectively
Austria, (Renner *et al*., 2020)	*n*=35 patients with SEA on mepo for 12 months or longer	[primary endpoint not specified]	• Median ACT score of 12.5 at baseline increased to 19 (15–22.5) • Median increase in FEV1 at week 4 was 0.09 (IQR -0.09−0.32; *P*<0.05) • Reduction of median steroid doses from 6.25 mg daily (IQR 0–20) at baseline to 2.5 mg daily (IQR 0–11.9) at week 8 (*P*<0.001) • Median eosinophils value reduced from a 0.30×10^9/L (IQR 0.11–0.5×10^9/L) to 0.07×10^9/L (IQR 0.04–0.12×10^9/L) already at week 4 (*P*<0.001)

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Table 1: Contd...

Study	Patients and Intervention	Primary endpoint	Key secondary outcomes
		RWE studies	
Italy, (Crimi *et al*., 2020)	*n*=31, patients SEA and one or more comorbidities (nasal polyps, allergic rhinitis, gastro-esophageal reflux disease, nonallergic rhinitis with eosinophilia syndrome, obesity, bronchiectasis), Mepo 100 mg Q4W SC for at least 12 months	[primary endpoint not specified]	• Median blood eosinophil count decreased from 791 cells/uL (IQR 420–1300) to 80 cells/ul (IQR 43–109) at 12 months (P<0.0001) • Significant change in mean predicted FEV1 at 12 months vs baseline (2.12±0.75 vs 2.33±0.7; P=0.0224) • Significant improvement in ACT at 12 months vs baseline (13.65±4.54 points vs 21.29±4.49; P<0.0001) • Proportion of patients on oral CS significantly reduced 67.7% vs 16.1% (P<0.0001) • Significant difference in the number of exacerbations/year (6, IQR 4–12, vs 0, IQR 0–1; P<0.00001). Neither the comorbidities nor other characteristics (sex, BMI, age, smoking) influenced treatment response
Spain, (Loli-Ausejo *et al*., 2023)	*n*=44 patients Mepo 100 mg Q4W SC (at least 6 doses)	Effectiveness of mepo • Asthma exacerbations decreased by 70.2% over 12 months • Asthma exacerbations requiring hospitalization decreased by 71.9% over 12 months	• FEV_1 increased by 0.29 L (range, -0.79–1.21 L) • Median (IQR) annual cumulative dose of oral CS decreased from 900 mg (555−2565 mg) in the previous year to 0 mg (0.0−1364 mg) • ACT scores increased from 13.9 to 20.1
Italy, (Crimi *et al*., 2021)	*n*=32, patients with SEA and co-presence of bronchiectasis on mepo for 1 year Mepo 100 mg Q4W SC	[primary endpoint not specified]	• ACT score significantly improved from baseline, after 6 months in both SEA (13.8±4.6 to 20.7±4.1, P=0.0009) and SEA+bronchiectasis (13±4.8 to 20.7±4.6, P=0.0003) group • Exacerbations/year significantly reduced, 8 (4–12) to 0 (0–1) in SEA+bronchiectasis and from 7 (4–12) to 0 (0.00–0.75) in SEA, respectively (P<0.0001) • Daily oral CS dose significantly decreased from 15 mg (0–25) to 0 mg (0−0) in SEA+bronchiectasis group (P=0.003) and from 8.8 mg (0–25) to 0 mg (0−0) in SEA alone group (P=0.01) • Mean predicted FEV1 significantly improved in SEA+bronchiectasis group (p=0.02) • Sputum eosinophil count significantly reduced from 26.5% (10.8–62.8) to 12.5% (5–23) (P<0.0001) in SEA + bronchiectasis group and from 20.5% (17.3–42.3) to 9% (7–10) (P<0.0001) in SEA group
USA (Corren *et al*., 2022)	*n*=351, patients SEA and receiving high dose intranasal CS and mepo	[primary endpoint not specified]	Use of inhaled CS in each quarter of 12-month follow-up period • High dose intra-nasal CS decreased in quarters 1 to 4 after mepo initiation (79.8%, 74.6%, 68.9%, 65.5%, respectively) • 49.0% reduced or discontinued inhaled CS for one or more quarter
France Early Access Program (Taillé C *et al*., 2020)	*n*=146 Mepo 100 mg SC Q4W	Profile of patients participating in Early Access Program	• Number of exacerbations reduced from 5.8/patient/year at baseline, to 0.6/patient/year • Need for hospitalization reduced from 0.6/patient/year to 0.1/patient/year • Need for emergency department visits reduced from 0.5/patient/year to 0.1/patient/year • Patients using oral CS reduced from 92.8% to 34.7% by 24 months

ACQ, Asthma Control Questionnaire; ACT, asthma control test; AE, adverse event; AMR, asthma medication ratio; AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; CI, confidence interval; CS, corticosteroid; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume 1s; IV, intravenous; IQR, interquartile range; mepo, mepolizumab; PBO, placebo; Q4W, every 4 weeks; QoL, quality of life; RWE, real-world evidence; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; SEA, severe eosinophilic asthma; VAS, Visual Analogue Scale; vs, versus

loss of asthma control, suggesting extended and continuous treatment in patients with severe disease.[46]

Safety

As with efficacy parameters, there have also been studies evaluating the long-term safety of mepolizumab in patients with SEA. Across studies, the most frequently reported adverse events (AEs) were nasopharyngitis, asthma, bronchitis, upper respiratory tract infections, and headache.[24,26,47,48] In the COSMOS study, 86% and 14% of patients reported on-treatment adverse events (AEs) and serious AEs, respectively (note that serious AEs were considered related to study treatment in <1% of patients); ≤4% of patients experienced systemic or local site reactions.[48] In the COSMOS extension study, COSMEX, 93% of patients reported on-treatment AEs. Treatment-related AEs and injection-site reactions were reported by 15% and 4% of patients,

respectively.[47] The incidence of injection-site reactions was more frequent in the SC mepolizumab group (9%) than in the IV mepolizumab group or the placebo group (3% in both).[24] Infusion-related reactions were reported in ≤12% of patients, regardless of mepolizumab dose.[26] Also, RWE studies including REALITI-A and REDES did not report any new or unexpected safety signals.[21,35]

Eosinophilic granulomatosis with polyangiitis (EGPA)

The global estimated prevalence of EGPA ranges from 2 to 38 cases per million individuals, while the estimated incidence varies from 0.18 to 4.0 cases per million person-years, depending on the geographic region and the specific diagnostic criteria used.[49] EGPA, traditionally known as Churg-Strauss syndrome, is characterised by asthma, eosinophilic infiltrations leading to eosinophilia, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis that majorly affects small or medium vessels. Though the contribution of ANCA in the pathogenesis of vasculitis is considered crucial, the positivity rate of ANCA in patients with EGPA is only 30% to 40%,[50] leading to two phenotypes of EGPA: ANCApositive and ANCAnegative. Thus, pathophysiology of EGPA appears to overlap among the immune mechanisms that contribute to vasculitis and the pathological processes leading to eosinophilic syndromes.[51] Hence, the use of mepolizumab was considered in addition to long-term oral/systemic CS treatment to manage refractory asthma and allergic symptoms in EGPA. Currently, mepolizumab in combination with glucocorticoids is the first-line treatment for EGPA.[52]

Clinical development and efficacy

Mepolizumab was used to treat EGPA in a case report,[53] a small open-label pilot study (n = 7),[54] and an uncontrolled study in patients with relapsing or refractory EGPA (n = 10), where it permitted the safe reduction of glucocorticoid doses and showed reduced eosinophilic counts in EGPA.[55] Both studies used mepolizumab 750 mg IV dose, and discontinuation led to relapses or recurrence of EGPA manifestations. The phase 3 MIRRA study (n = 136) in patients (on a prednisone dose of 7.5–50 mg) with relapsing or refractory EGPA who received mepolizumab (300 mg Q4W SC) or placebo for 52 weeks, reported that 28% versus 3% of patients, respectively, achieved a primary endpoint of 24 weeks [defined as a Birmingham Vasculitis Activity Scale (BVAS) of 0; prednisone dose < 5 mg/day] of accrued remission [Table 2].[56] The remission persisted at weeks 36 and 48 in the mepolizumab arm versus placebo. Relapse rates were reduced by half and had a substantial steroid-sparing effect with prednisone dose reductions to 4 mg/day in 44% patients and 18% discontinued prednisone.[56] Of the total population of the MIRRA study, 19% (26/136) of patients were ANCA-positive at baseline. A larger proportion of the patients were at remission at week 36 and week 48 with mepolizumab versus placebo (ANCA-positive: 54% vs 0%; without ANCA-positive: 27 versus 4%, respectively) irrespective of ANCA status. These landmark findings from the MIRRA study resulted in the approval of mepolizumab as the first FDA-approved drug for EGPA. A *post hoc* analysis of MIRRA reported that the clinical benefit was achieved in 87% of patients in mepolizumab versus 53% in the placebo group.[57] Based on these findings, the American College of Rheumatology/Vasculitis Foundation guidelines (2021) recommended mepolizumab + glucocorticoids as a first-line treatment for active/non-severe EGPA.[52]

Overall, the clinical benefits linked with reduced eosinophils, better clinical outcomes, and CS-sparing activity in EGPA support the use of mepolizumab as a first-line treatment in addition to CS.

Real-world evidence of efficacy

Several real-world observational or retrospective studies demonstrated efficacy of mepolizumab in real-world clinical practice [Table 2]. In Japanese patients (n = 16) with relapsing or refractory EGPA resistant to CS, mepolizumab given SC over 12 months at 300 mg Q4W resulted in a 12-month remission rate of 75% and reduction in CS dose (1655 vs 2665 mg/year) versus pre-mepolizumab as well as reduction in BVAS, symptoms (ear, nose, and throat), and eosinophil counts.[58] In a retrospective European study in EGPA patients (n = 51), administration of mepolizumab at 100 mg Q4W and 300 mg Q4W SC doses resulted in 12-month remission rates of 76% and 82%, respectively, with overall remissions observed in 78% of the patients.[59] However, another observational study in a larger number of European patients (n = 203) showed a lower response rate (12-month remission rate = 30.4%) than those in the observational study by Canzian *et al*.[59] and the response rate was found to be higher amongst ANCA-negative versus ANCA-positive patients.[60] Another observational study with the majority of patients being ANCA-positive postulated that the low dose (100 mg vs 300 mg; Q4W) may be useful in reducing flares, exacerbations, treating asthma symptoms, and decreasing CS doses. Thus, apart from ANCA status, disease severity and symptoms at the initiation of the mepolizumab play a crucial role in overall remission rates with mepolizumab use.[61]

The efficacy of low dose SC mepolizumab (100 mg Q4W) has been established in a retrospective study with the same benefit as high dose (300 mg Q4W)[62] to treat the long-lasting peripheral neuropathy in EGPA patients.[63] Induction remission therapy of mepolizumab (versus cyclophosphamide) in patients with severe EGPA has demonstrated a higher retention rate (100% versus 61.5%) and lower AEs (28.6% versus 53.8%) in the mepolizumab group.[64]

Switching from rituximab to mepolizumab has been found to be beneficial in reducing asthma attacks, sustaining remission, and exhibiting CS dose reductions.[65] Remission rates of 38.8% and 57.1% at 12 and 24 months, respectively, were reported in a recent 2-year observational study

Table 2: Clinical trial and RWE data with mepolizumab in EGPA

Study	Patients and Intervention	Primary endpoint	Key secondary outcomes
Randomized clinical trials and *post-hoc* studies			
MIRRA (Wechsler *et al*., 2017)	*n*=68, PBO; *n*=68, mepo 300 mg SC Q4W for 52 weeks for 52 weeks	Accrued weeks of remission over 52 weeks and proportion of participants in remission at both week 36 and 48 • 24+ weeks of accrued remission in 28% vs 3% with mepo vs PBO (OR, 5.91; 95% CI, 2.68–13.03; *P*<0.001) • Remission at week 36 and 48: 32% vs 3% with mepo vs PBO (OR, 16.74; 95% CI, 3.61–77.56; *P*<0.001)	• Relapse rates were reduced by 50% • Prednisone dose was reduced to 4 mg/day in 44% patients and 18% discontinued prednisone
A *post-hoc* analysis of MIRRA (Steinfeld *et al*., 2019)	*n*=68, PBO; *n*=68, mepo 300 mg SC Q4W for 52 weeks	Clinical benefit (remission at any time)	• Remission rate for mepo versus PBO were 78% versus 32% in patients with BVAS 0 and ≤4 mg/d glucocorticoid • Remission rate for mepo versus PBO were 87% versus 53% in patients with BVAS 0 and ≤7.5 mg/d glucocorticoid, *P*<0.001
RWE studies			
Japan (Ueno *et al*., 2021)	*n*=16; patients with relapsing or refractory EGPA resistant to CS post mepo 300 mg Q4W SC for 12-months.	12-month remission rate • 75% at month 12	• Significant reduction in BVAS and eosinophil count • Reduction in CS dose (1655 mg/year) in the post-mepo group vs pre-mepo group (2665 mg/year) • Decreased disease activity • Mepo retention rate was 100%
Europe (Canzian *et al*., 2021)	*n*=51 100 mg Q4W and 300 mg Q4W SC for 12-month	[primary endpoint not specified]	• 12-month remission rates of 76% and 82% for 100 mg/monthly and 300 mg Q4W SC doses, respectively • Highly effective in glucocorticoid-dependent asthma
Europe (Bettiol *et al*., 2022)	*n*=203 100 mg Q4W and 300 mg Q4W SC	[primary endpoint not specified]	• The 3-month, 12-month, and 24-month complete response rates were 25%, 30.4%, and 35.7%, respectively • Complete response rates were comparable rates between mepo 100 mg and 300 mg dose groups • Significant reduction in BVAS score, prednisone dose, and eosinophil counts
Rios-Garces *et al*., 2022	*n*=11 100 mg Q4W and 300 mg Q4W SC for 3–66 months	[primary endpoint not specified]	• BVAS=0 in 100% patietns at 12 months or earlier • Improvement in disease activity • Notable glucocorticoid tapering
Ozturk *et al*., 2022	*n*=25 100 mg Q4W SC for 12-month (low dose evaluation)	[primary endpoint not specified]	• Reduction in oral CS dose from 11.04 mg to 3.65 mg • Reduction in asthma exacerbations • Reduction in blood eosinophil count • The 6-month and 12-month remission rates were 76% and 81.25%, respectively • Mean FEV_1 increased from 1.88 L to 2.46 L at 12 months • Improved sinonasal and asthma outcomes
Nakamura *et al*., 2022	*n*=13 patients with conventional treatment-resistant peripheral neuropathy 100 mg Q4W SC for 12-month (low dose evaluation)	Change from baseline in peripheral neurological symptoms (VAS) at 12 months • VAS scores significantly improved for: • Pain from 67.0 to 48.0, *P*=0.012 • Numbness from 67.0 to 51.0, *P*=0.017	• Reduction in urinary levels of eosinophil-derived neurotoxin
Ueno *et al*., 2022	*n*=20 patients on high dose CS + mepo or high dose CS + IV cyclophosphamide 300 mg Q4W SC	Mepo retention rate • Retention rate with mepo vs cyclophosphamide 100% vs 61.5%, respectively	• Lower AEs (28.6% vs 53.8% in cyclophosphamide group) in mepo group • Significant reduction in concomitant CS dose within 3-month treatment in mepo group

BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; CS, corticosteroid; EGPA, eosinophilic granulomatosis with polyangiitis; mepo, mepolizumab; OR, odds ratio; PBO, placebo; Q4W, every 4 weeks; VAS, Visual Analogue Scale; vs, versus

in patients with relapsing-refractory EGPA receiving mepolizumab and benralizumab. Among patients dependent on oral CS, 69.6% reduced CS daily dose by 75% and 28.3% discontinued CS.[66]

These real-word data corroborate the clinical efficacy of mepolizumab and have proved it as a remission induction therapy for EGPA. Although the dose of 300 mg Q4W for MIRRA was based on data collected from 16 mepolizumab

studies across various eosinophilic diseases, the real-world data indicate that the lower dose of 100 mg Q4W may also be useful in EGPA, but further evidence is warranted.

Safety

Throughout the clinical development stage, the rates of AEs were similar between mepolizumab and other treatment arms in EGPA clinical studies. The most frequently observed AEs were headache, upper respiratory infection, nasopharyngitis, and local injection-site reaction.[56] Real-world data did not signal any new or severe safety signal for mepolizumab, which was used safely at 100/300 mg doses.

Hyper-eosinophilic syndrome (HES)

HES is a rare, debilitating heterogeneous group of disorders characterised by persistently elevated blood ($\geq 1.5 \times 10^9$ cells/L) or tissue eosinophil counts and demonstrating a major contribution of eosinophils in organ damage.[5] Although the precise global prevalence of HES is unknown, it is estimated to be 0.3–6.3 and 0.15–0.89 cases per 100,000 person-years in the US[67] and in the UK, respectively.[68] Treatment choices for HES are limited and generally include CS along with cytotoxic or immunosuppressive agents.[69] Therefore, to optimize the HES treatment strategies that could prevent further organ damage, use of anti-IL-5 therapies such as mepolizumab was considered.

Clinical development and efficacy

Mepolizumab was first used in HES in a case series in 2003 and in a small open-label uncontrolled study showing effective reduction in blood eosinophil counts and CS-sparing effect.[70] From 2005, mepolizumab was offered for compassionate use (NCT00244686). In 2008, in a phase 3 study (n = 85) (NCT00086658), treatment with mepolizumab IV infusions of 750 mg Q4W versus placebo reduced the daily prednisone dose (6.2 mg versus 21.8 mg), and a higher proportion of CS-dependent patients (20–60 mg/day) with HES without FIP1L1-PDGFRA gene stopped prednisone entirely (47% versus 5%).[71] Another landmark phase 3 study (n = 108) (NCT02836496) showed a 50% reduction in patients experiencing flares or withdrawals, a 66% risk reduction for both, first flares and in annualised flare rates with mepolizumab (300 mg SC) compared to placebo in FIP1L1-PDGFRA-negative HES patients [Table 3].[72]

Mepolizumab therapy has been promising for glucocorticoid-sensitive patients with treatment-refractory or severe or idiopathic or lymphocytic HES,[73] but for myeloid forms of HES, results have been quite discouraging.[74] Thus, further understanding of clinical presentation of HES and efficacy of mepolizumab will help to optimise the use of mepolizumab to treat HES effectively.

Real-world evidence of efficacy

A retrospective analysis of 103 patients who started on ≥700 mg dose of mepolizumab had higher pre-biologic daily prednisone requirements but showed similar reductions in prednisone (CS) use compared to those starting on 100 mg dose. However, dose adjustments (higher or lower than the earlier dose) and a decrease in the frequency of mepolizumab administration (from Q4W to every 5 to 12 weeks) were also noted during the study. Although these findings highlight the variability in treatment response and the need for individualized approaches in managing HES, further studies are needed to support these findings.[75] A *post hoc* analysis of data from the mepolizumab HES compassionate use program spanning over a decade, indicated that the peak absolute eosinophil count, sensitivity to oral CS, pulmonary involvement, serum IL-5 levels, and clinical subtype of HES may be associated with response to mepolizumab treatment in severe HES cases.[74] As mepolizumab approval for treating HES is recent, it will be interesting to see the real-world data from a larger population with HES.

Safety

In the pivotal phase 3 study of mepolizumab in patients with HES, the most commonly reported AEs were fatigue, pruritis, headache, and arthralgia.[71] Cough, fatigue, headache, upper respiratory tract infections, and sinusitis were most commonly reported in the open-label extension study (n = 78).[76] The study reported non-fatal serious AEs possibly related to mepolizumab in three patients and one fatal case of angioimmunoblastic T-cell lymphoma.[76] In the post-compassionate use study, AEs were similar between the placebo and mepolizumab groups, with no severe AEs linked to mepolizumab. The common AEs included bronchitis, upper respiratory tract infection, headache, and nasopharyngitis.[72]

Chronic rhinosinusitis with nasal polyps (CRSwNP)

CRSwNP is an upper airway disease with persistent eosinophilia characterised by nasal blockage or discharge, anosmia, severe discharge, and facial pain due to thickening of nasal mucosa, and the formation of polyps.[77] The prevalence of chronic rhinosinusitis (CRS) in the US and Europe is estimated to be 2.1% to 4.3%, respectively, with 20% to 30% of patients suffering with CRSwNP.[78] The traditional treatment option for CRSwNP includes intra-nasal or oral CS.[1] When these treatments fail, nasal surgeries are performed, but recurrence of nasal polyps is common[79,80]; thus, there is a need for additional treatment options.

Clinical development and efficacy

The use of mepolizumab in CRSwNP was established based on two observations: 1) Mepolizumab has shown better asthma outcomes as well as improvements in nasal symptoms of patients with SEA[32,81] and 2) polyp recurrence post surgical therapy has been correlated with eosinophilic inflammation.[82]

Early studies of mepolizumab in patients with CRSwNP demonstrated a reduction in nasal polyp scores, which can range from 0 (no visible nasal polyps) to 4 (polyps

completely obstructing the nasal cavity) for each nostril, reduction in blood eosinophil counts,[83] improved symptoms, and a lower need for surgery.[84] The phase 3 SYNAPSE study (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab) (n = 407) reported significant reductions in the endoscopic nasal polyp score and nasal obstruction visual analog scale (VAS) score in the mepolizumab group (SC 100 mg Q4W) versus placebo in patients with severe recurrent/refractory CRSwNP with high symptom burden and previous nasal polyp surgeries [Table 4].[85]

Real-world evidence of efficacy

Several RWE studies in patients with CRSwNP demonstrated that mepolizumab significantly reduced

Table 3: Clinical trial and RWE data with mepolizumab in HES

Study	Patients and Intervention	Primary endpoint	Key secondary outcomes
Randomized clinical trials and *post hoc* studies			
Rothenberg *et al*., 2008	*n*=42, PBO; *n*=43, mepo 75 mg Q4W IV in CS-dependent patients (20 to 60 mg/day) with HES for 36 weeks	Reduction of daily prednisone dose to ≤10 mg for ≥8 weeks • Reached in 84% vs 43% patients on mepo vs PBO, respectively • HR=2.90; 95% CI, 1.59–5.26; *P*<0.001	• Daily prednisone dose was reduced (6.2 mg vs 21.8 mg) in mepo vs PBO group • 47% vs 5% in mepo vs PBO group patients were prednisone free • Bood eosinophil count <600 cells/μL was reached in 95% vs 45% patients with mepo vs PBO (*P*<0.001) • Eosinophil-derived neurotoxin levels were significantly lower with mepo vs PBO
Roufosse *et al*., 2020	*n*=54, PBO; *n*=54, mepo 300 mg Q4W SC for 32 weeks	Proportion of patients experiencing a flare • 50% fewer patients experienced a HES flare with mepo vs PBO (28% vs 56%; *P*=0.002)	• Risk of experiencing a first flare was 66% lower for mepo vs PBO (*P*=0.02) • Adjusted annualized rate of flares was 66% lower with mepo vs PBO (*P*<0.001) • Blood eosinophil count was reduced from baseline to week 32 by 92% with mepo vs PBO
RWE studies			
Compassainate use reptrospective study (Chen *et al*., 2022)	*n*=103 100 mg to 700 mg IV	[primary endpoint not specified]	• Improved HES symptoms • Hematologic remission in >90% patients • Highest CS dose reductions with mepo compared to other biologics • 86% patients showed improvement in one or more pulmonary signs or symptoms • Organ-specific improvements: dermatologic (77%), gastrointestinal (74%), and constitutional (67%) • Mepo administration frequency reduced from Q4W to every 5 to 12 in seven patients

CI, confidence interval; CS, corticosteroid; HES, hyper-eosinophilic syndrome; IV, intravenous; mepo, mepolizumab; NP, nasal polyp; PBO, placebo; Q4W, every 4 weeks; RWE, real-world evidence; SC, subcutaneous; vs, versus

Table 4: Clinical trial and RWE data with mepolizumab in CRSwNP

Study	Patients and intervention	Primary endpoint	Key secondary outcomes
Randomized clinical trials and *post-hoc* studies			
SYNAPSE Han *et al*., 2021	*n*=201, PBO; *n*=206, mepo 100 mg SC Q4W for 52 weeks in patients with severe recurrent/refractory CRSwNP for 52 weeks	Change from baseline in endoscopic NP score and in nasal obstruction VAS • Endoscopic NP score improved in mepo vs PBO−0.73 (95% CI, −1.11, −0.34; *P*<0.0001) • Nasal obstruction VAS score improved in mepo vs PBO−3.14 (−4.09, −2.18; *P*<0.0001)	• Time to first nasal surgery up to Week 52 in mepo vs PBO: Hazard ratio 0.43 (95% CI, 0.25, 0.76; *P*=0.0032)
RWE studies			
Turkey (Yilmaz *et al*., 2020)	*n*=16; patients oral CS-dependent SEA-CRSwNP 100 mg Q4W SC for at least 24 weeks.	[primary endpoint not specified]	• Daily CS dosage was reduced from baseline in all patients • At week 24 CS was discontinued in 40% of the patients (baseline mean steroid dose: 9.2±5.2 mg, week-24: 1.3±1.4 mg; *P*<0.001) • At week 24 asthma exacerbations decreased significantly (2.1±2.7 vs 0.07±0.26; *P*=0.012) • Significant increase in ACT scores (baseline mean ACT: 18±5.7; 24th week mean ACT: 23.3±3; *P*=0.006) • NAS decreased from baseline (5.6±4.4) to week 24 (3.2±3.2) *P*=0.021

ACT, asthma control test; CI, confidence interval; CRSwNP; chronic rhinosinusitis with nasal polyps; CS, corticosteroid; HES, hyper-eosinophilic syndrome; IV, intravenous; mepo, mepolizumab; NAS, numerical analog scale; NP, nasal polyp; PBO, placebo; Q4W, every 4 weeks; RWE, real-world evidence; SC, subcutaneous; SEA, severe eosinophilic asthma; VAS, visual analog scale; vs, versus

symptoms, nasal polyp scores, blood eosinophils, and systemic CS use, resulting in an increased HRQoL[86-88]; in one of these studies, outcomes with mepolizumab were superior to other biologics [Table 4].[88]

Treatment with mepolizumab has shown to reduce daily CS dosage and decreased asthma exacerbations in patients with CRSwNP-SEA.[81] Notably, several small real-world studies showed beneficial effects of mepolizumab in aspirin-exacerbated CRSwNP[89] and eosinophilic otitis media that are associated with severe uncontrolled CRSwNP.[90]

Safety

The most commonly reported AEs were common cold (early study),[83] headache, and nasopharyngitis (randomized trials).[84,85] Headaches, epistaxis, and nasopharyngitis were frequently reported in RWE studies.

CLINICAL PERSPECTIVE ON AWARENESS ABOUT EARLY INITIATION OF MEPOLIZUMAB/ TARGETED BIOLOGICS AMONGST EXPERTS

Traditionally, CSs are primarily used to treat eosinophilic conditions; however, the prolonged usage of CS carries a substantial burden of AEs and a risk of developing resistance. Early start of targeted biologic treatment may help reduce CS usage and attain optimal outcomes for the patient.[30,56,72,85]

In SEA, several clinical and real-world studies indicated the benefits of mepolizumab in terms of symptom reductions, reductions or discontinuation of daily CS maintenance doses, and better quality of life. DREAM and MENSA have laid down the initiation criteria for patients with SEA who may benefit from mepolizumab therapy: ≥2 exacerbations in the previous 12 months despite high dose CS and additional controller(s): an eosinophil count of ≥150 cells/mL at initiation or ≥300 cells/mL in previous 12 months. However, in the real world, most of the time, severe asthma progresses to similar comorbid conditions that demand increased maintenance CS therapy. Thus, the guidance regarding initiation of mepolizumab in comorbid patients with SEA is needed to decrease the CS burden and improve the quality of life.

EGPA, if left untreated or un/sub-diagnosed, may lead to organ damage similar to that of HES. The clinical and RWE studies reviewed here indicate that the remission induction in severe or non-severe EGPA can be achieved by high dose CS; however, the guidelines suggest a maximum of 7.5 mg prednisone daily. Recent biologics, such as mepolizumab, have already shown the CS-sparing effects in eosinophilic diseases including EGPA; thus, it might be a useful treatment strategy to initiate early combined treatment with biologics along with as low a dose of CS as possible to decrease CS exposure and avoid risk of relapses at the same time.[91]

Early treatment with effective biologics may be advantageous in HES as serious organ damage could ensue if treatment is delayed. Notably, HES is challenging to diagnose early due to symptom overlap with other conditions. Patients demonstrating severe eosinophilia along with organ damage must be investigated for the possibility of HES before initiating any specific treatment.[92] In the past, persistent eosinophilia for at least 6 months was required to establish the diagnosis of HES; however, the definition of HES has been revised to a 4-week observation interval.[5]

Overall, delaying treatment for eosinophilic conditions may result in the development of refractory severe disease or comorbid conditions that demand high dose CS and may lead to CS resistance. Physicians need to be aware of potential benefits of reducing the CS doses by combining them early with approved biologics, such as mepolizumab.

OTHER CURRENT ANTI-IL-5 TREATMENTS FOR EOSINOPHILIC CONDITIONS

In addition to mepolizumab, clinical studies of maintenance therapy with reslizumab and benralizumab provided further evidence of the therapeutic advantages of targeting the IL-5 pathway in patients with asthma. These studies demonstrated decreased exacerbations, enhanced lung function, CS-sparing effect, and improved quality of life and confirmed the correlation between baseline blood eosinophil counts and treatment response in SEA patients, similar to those in the mepolizumab studies.[93-96] Both reslizumab and benralizumab are approved by US FDA to treat SEA. Additionally, off-label use of benralizumab has shown improvement in refractory asthma or persistent ear, nose, and throat manifestations in EGPA patients.[94,97] Several ongoing clinical studies are assessing safety and efficacy of benralizumab and reslizumab to treat EGPA (NCT03010436, NCT04157348), CRSwNP (NCT05180357, NCT02799446), HES (NCT04191304), eosinophilic esophagitis (NCT04543409), and eosinophilic gastrointestinal disease (NCT03473977). The findings from these studies will further help establish the role of IL-5 and applicability of IL-5 treatments to treat these eosinophilic conditions.

CONCLUSION

The established role of IL-5 in eosinophilic disorders underscores its pivotal involvement in the pathophysiology of these conditions. Mepolizumab, an anti-IL-5 monoclonal antibody, has received approval as an adjunctive maintenance therapy for SEA, CRSwNP, EGPA, and HES. Robust clinical trials and real-world data have established the safety and efficacy of mepolizumab in SEA, CRSwNP, EGPA, and HES, with clinical benefits including symptom control, reduced exacerbations, decreased blood eosinophil counts, CS-sparing effects, and improved HRQoL. For HES, mepolizumab is the only available biologic treatment, whereas for EGPA, mepolizumab is

the approved first-line treatment along with low dose CS. Furthermore, corroboration of other IL-5 pathways targeting biologics providing therapeutic benefits and enhanced overall quality of life in asthma patients comes from studies with reslizumab and benralizumab. Ongoing clinical studies seek to further validate IL-5 targeting as a preferred adjunctive maintenance therapy across diverse eosinophilic disorders.

The early integration of biologics alongside CS represents a promising therapeutic strategy, offering reduced CS-dependence and mitigated risk of AEs; however, adaptation of this strategy in the real-world clinical practice is urgently needed.

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Author contributions

Dipti Gothi, Raghupathi Narasimhan, Randeep Guleria, and Manu Chopra, Aanchal Gvalani, and Rashmi Hegde have reviewed the data collected, contrinuted to the development and review of the draft. All authors approved the final version of the manuscript.

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Conflicts of interest

Dipti Gothi, Raghupathi Narasimhan, Randeep Guleria, and Manu Chopra declares no conflict. Aanchal Gvalani and Rashmi Hegde are employees of GSK.

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