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Efficacy and safety of mepolizumab in a real-world cohort of patients with severe eosinophilic asthma

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ABSTRACT

Background: The interleukin 5 (IL-5) pathway is an important component in the pathophysiology of severe eosinophilic asthma. Mepolizumab is a monoclonal antibody that targets the IL-5 pathway. Clinical trials showed efficacy of Mepolizumab in patients with severe eosinophilic asthma. However, reports on experience with treatment in a real-world cohort are limited.

Objectives: Evaluation of the efficacy and safety of Mepolizumab for treatment of severe eosinophilic asthma in a real-world cohort of patients.

Methods: A clinical prospective observational trial included all patients >18 years treated with Mepolizumab between March 2016 to March 2019 at Rabin Medical Center. The composite primary outcome measures evaluated: increase in FEV1 by ≥ 200 ml and/or decrease in exacerbation rate of $\geq 50\%$ and/or cessation of oral corticosteroids (OCS) treatment or $\geq 50\%$ decrease in dosage. Also evaluated: blood eosinophil count, adverse events and quality of life.

Results: Of 61 patients, 50 (82.0%) achieved the primary outcome. The number of patients who suffered from frequent exacerbations decreased from 52 (85.2%) to 8 (13.1%) ($p < 0.001$). Twenty-two patients (68%) stopped OCS treatment or received $>50\%$ reduced dosage ($p < 0.001$). Mean FEV1 increased from 1.72 ± 0.78 liters to 1.87 ± 0.85 liters ($p = 0.043$). Response to therapy was seen within six months. Forty-nine patients (80%) reported an improvement in quality of life ($p < 0.001$). Only minor adverse events were reported.

Conclusion: Treatment with mepolizumab was well tolerated and significantly lowered the exacerbation rate and OCS dependence in a real-world cohort of severe eosinophilic asthma patients. Response to therapy was within six months and treatment effect was sustained over time.

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Background

Severe asthma is defined as asthma which requires treatment with high dose inhaled corticosteroids with a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite therapy. Its prevalence is estimated at 5–10% of the total asthma population. A subgroup of patients with severe eosinophilic asthma, suffer from frequent exacerbations with limited response to treatment (1,2). The interleukin 5 (IL-5) pathway is an important component in the pathophysiology of severe eosinophilic asthma. By binding to its receptor on eosinophils, IL-5 stimulates the production of transcription factors that increase proliferation and inhibit apoptosis and thus increase eosinophil production in the bone marrow. It also promotes eosinophil maturation locally in the airways and increases activation, proliferation and survival of

eosinophils (3–8). IL-5 signaling is therefore an attractive target for asthma treatment. Three anti IL-5 monoclonal antibodies are currently approved for asthma treatment: mepolizumab (trade name Nucala; GlaxoSmithKline), reslizumab (trade names Cinqair or Cinquaero; Teva) and benralizumab (MedImmune or Fasenra; AstraZeneca). Mepolizumab and reslizumab both target IL-5, whereas benralizumab binds to the alpha chain of the IL-5 receptor (IL-5R α), found on eosinophils and basophils.

In clinical trials, treatment with anti-IL-5 has demonstrated decreased exacerbation rates and lowered oral steroid dosing (9–11). Evaluation of these drugs in clinical trials showed superior efficacy in comparison to placebo (9–17). However, reports on experience with treatment in a real-world cohort are limited. Mepolizumab for severe eosinophilic asthma was approved in Israel in 2016 and was incorporated into

the Israeli basket of health services in 2017. Our aim was to evaluate the efficacy and safety of Mepolizumab in a real-world cohort of patients treated in Rabin Medical Center.

Methods

Design

This clinical observational prospective study included all patients >18 years who were treated with Mepolizumab in Rabin Medical Center from March 2016 through May 2018. Mepolizumab was administered by subcutaneous injection in a dose of 100 mg, once a month. The research study had no influence on the decision to treat the patient and the only inclusion criterion was continuous treatment with Mepolizumab for at least three months.

Data collection

The patients were followed prospectively from the first dose. Blood eosinophil levels, forced expiratory volume in 1 s (FEV1), oral corticosteroids (OCS) dosage, if maintenance therapy was given and adverse events were collected. We also examined all general practitioner (GP) and emergency room (ER) visits during the year before and one year after mepolizumab treatment, to assess the annual exacerbation rate. Finally, we interviewed each patient to evaluate quality of life (QoL).

Outcomes

Primary outcome

The composite primary outcome measures evaluated were

1. Increase in FEV1 by ≥ 200 ml. FEV1 was analyzed by calculating the mean in the last three months of treatment compared to the baseline FEV1 before initiation of treatment.
2. Exacerbation rate: only patients with two or more exacerbations during the year before therapy were considered for assessment according to the following criteria
 - a. For patients with two exacerbation in the year prior to therapy initiation, a positive outcome was considered, if they had no exacerbations in the year after mepolizumab commencement.
 - b. For patients with three exacerbations in the year prior to therapy initiation, a positive

outcome was considered, if they had one or no exacerbations in the year after mepolizumab commencement.

- c. For patients with an annual exacerbation rate of four or more, a positive outcome was considered, if the annual exacerbation rate decreased by at least 50% after mepolizumab commencement.

An exacerbation was defined as an ER visit, oral glucocorticoid treatment prescribed by a GP, if the patient did not receive oral prednisone maintenance therapy or glucocorticoid treatment prescribed by a GP in a dose that was twice or more the maintenance dose.

3. A decrease in maintenance OCS dosage by 50% or more.

Fulfilling at least one of the three components of the primary outcome was considered as treatment success.

Secondary outcomes

Each of the components of the primary outcome were also evaluated independently, as secondary outcomes. Additional secondary outcomes were blood eosinophil level, calculated monthly and as median of the first 3 months, as well as a subjective report of QoL assessed on a scale of -2 to 2 representing marked worsening, minor worsening, no change, minor improvement and marked improvement, respectively. We also evaluated adverse events. The study was approved by the Institutional Review Board ethics committee.

Statistical analysis

The components of the primary and secondary outcomes were analyzed with the McNemar's tests, paired T test and the Wilcoxon signed-rank test, as appropriate. The blood eosinophil level and quarterly exacerbation rates were analyzed with the Friedman Test for repeated measurements. *Post hoc*, between group analysis was done with paired Wilcoxon signed ranks test and Bonferroni correction for multiple comparisons.

Results

Sixty-one patients were treated with Mepolizumab at Rabin Medical Center for three months or more during the study period. The mean age was 57.46 ± 13.23 years, 35 participants were females (57.4%). The median follow-up period was 13.5 months (range 3–36) (Table 1). Fifty (82%)

patients achieved the primary outcome; 4 patients (6.6%) achieved all 3 components of the primary outcome, 24 patients (39.3%) achieved 2 components and 22 patients (36.1%) achieved one component (Table 2). Frequent exacerbations occurred in 52 patients (85.2%) before treatment initiation. Of those, 44 (84.6%) had a cessation of exacerbations or more than 50% reduction in the annual exacerbation rate after treatment commencement ($p < 0.001$). Overall, the yearly exacerbation rate decreased from 3.14 ± 2.28 in the year prior to therapy initiation to 0.85 ± 1.06 in the year after treatment commencement ($p < 0.001$). Thirty-two patients (52.5%) were on maintenance OCS before mepolizumab treatment. Of these, 22 (68%) discontinued OCS treatment or received $>50\%$

Table 1. Demographic and baseline characteristics.

Number of patients	61
Age (mean $\pm$ SD)	57.46 $\pm$ 13.23
Female sex (%)	35 (57.4)
Follow up time in moths (median + IQR)	13.5; 8.0–18.5
Baseline FEV1 (mean $\pm$ SD)	1.72 $\pm$ 0.78
Baseline eosinophil count cells/microL (median + IQR)	630; 400–900
Oral corticosteroid therapy (%)	32(52.5)

Table 2. Response to treatment with mepolizumab.

	N	%
Overall response	50	82.0
Number of components of the primary outcome*		
3/3	4	6.6
2/3	24	39.3
1/3	22	36.1
No response	11	18.0

* Primary outcome:

- Increase in FEV1 by ≥ 200 ml.
- Cessation or $\geq 50\%$ reduction in annual exacerbations rate from treatment commencement.
- Decrease in dose of $\geq 50\%$ or cessation of glucocorticoid treatment.

reduced dosage ($p < 0.001$) after mepolizumab treatment commencement. Overall, the median OCS dose decreased from 20 mg (IQR 6.25–40) before treatment initiation to 5 mg (IQR 0–9.37) after treatment commencement. Mean FEV1 increased from 1.72 ± 0.78 liters prior to mepolizumab treatment to 1.87 ± 0.85 liters ($p = 0.043$) after treatment initiation. Sixteen patients (26.2%) had an improvement in FEV1 of 200 ml or more. To assess response time and treatment efficacy over time, the yearly exacerbation rate before and after treatment commencement was divided into three-month periods. The mean exacerbation rate in all eight periods was then compared between groups; this analysis showed a statistically significant change in exacerbation rate six months after commencement of mepolizumab therapy and a lasting effect that did not change over time. All patients who responded to therapy did so within 6 months, no additional responders were seen after this time period (Figure 1). The median blood eosinophil level decreased from 630 cells/microL (IQR 400–900) at baseline to 100 cells/microL (IQR 64–200) after 3 months of therapy ($p < 0.001$). Repeated measures analysis showed a significant reduction in blood eosinophil count with a major and significant difference in the first month of therapy, in comparison to all other months of treatment ($p < 0.001$) (Figure 2). Overall 49 patients (80%) reported an improvement in QoL. 38 patients (62.3%) reported a major improvement in QoL, eleven patients (18%) reported a mild improvement of QoL and 9 patients (14%) reported no change in QoL, none of the patients reported a worsening in QoL (Table 3). No major adverse events were reported during this trial. Eleven patients (18%)

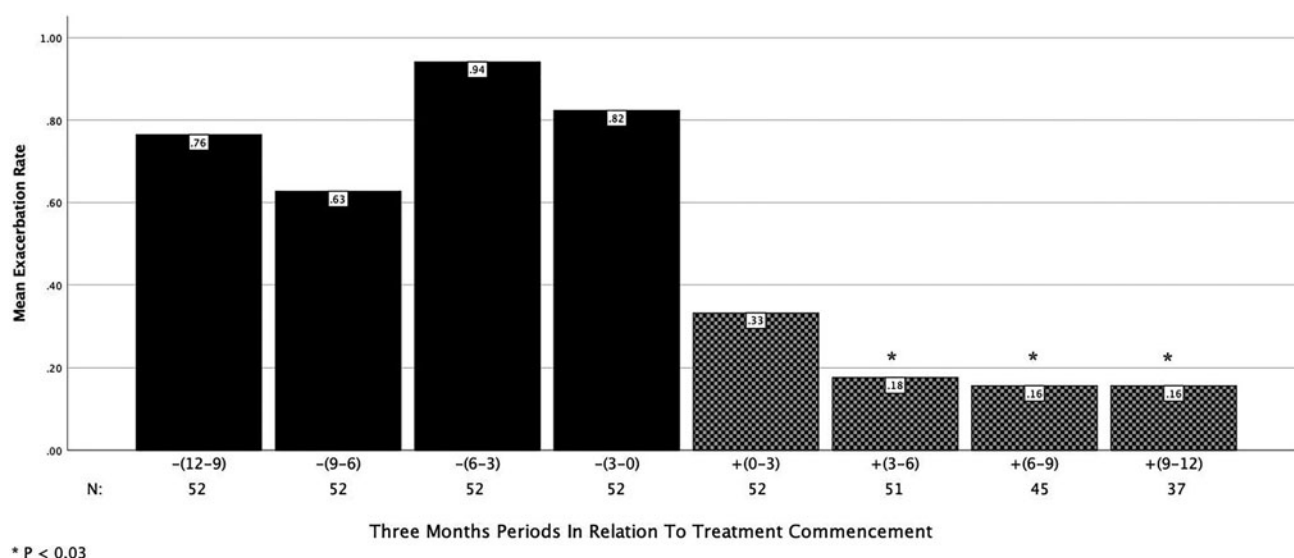


Figure 1. Quarterly exacerbation rates before and after treatment commencement.

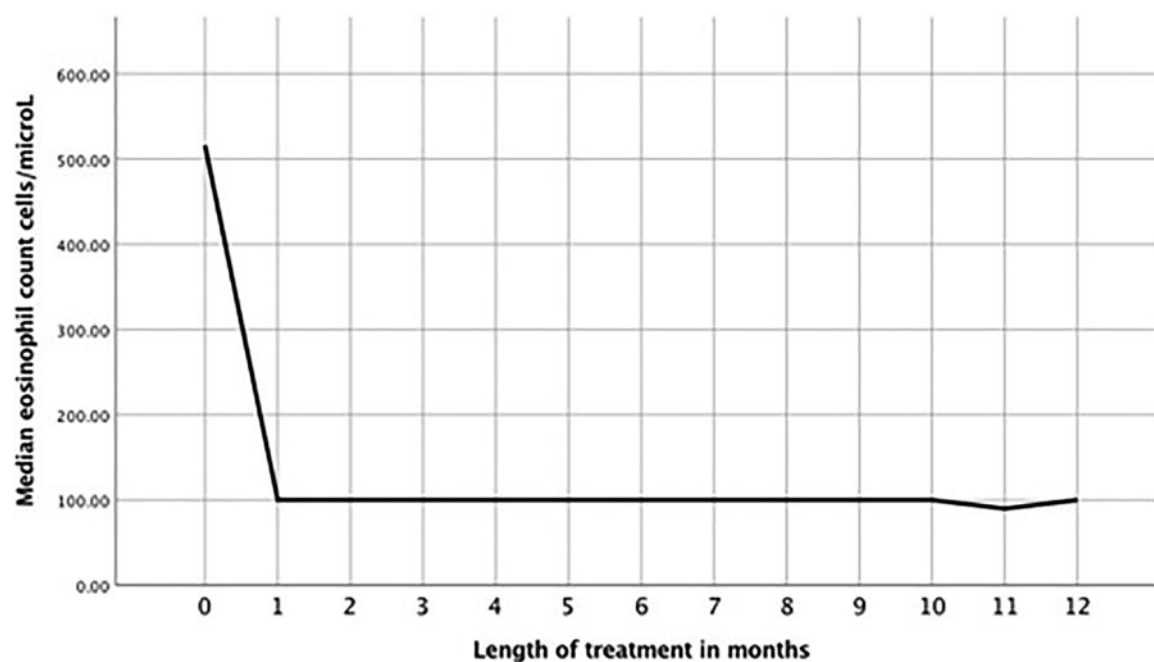


Figure 2. Median eosinophil count during treatment with mepolizumab.

Table 3. Summary of efficacy outcomes.

	Before treatment	After treatment	<i>p</i> value
Number of patients treated with maintenance OCS	32(52.5)	10 (16.3)*	<0.001
Mean FEV1	1.72 ± 0.78	1.87 ± 0.85**	0.043
Number of patients with Frequent exacerbations	52 (85.2)	8 (13.1)	<0.001
Annual exacerbation rate	3.14 ± 2.28	0.85 ± 1.06	<0.001
Eosinophil count cells/microL (median + IQR)	630; 400–900	100; 64–200#	<0.001
Quality of life			<0.001
	Marked improvement	38 (62.3%)	
	Minor improvement	11 (18%)	
	No change	9 (14%)	
	Minor worsening	0	
	Marked worsening	0	

*Patients who are still on maintenance OCS and did not decrease dose by more than 50%.

**Mean of last 3 months of treatment.

#Mean of first 3 months of treatment.

OCS: Oral corticosteroids; IQR: Inter quartile range.

reported mild adverse events including muscle pain, pruritus, rash, injection site pain, fever and headache.

Discussion

The present study reports the first Israeli experience with mepolizumab treatment in a real-world cohort of patients with severe eosinophilic asthma. The results showed an 82% response rate, a significant reduction in exacerbation rate and a significant reduction in OCS dose. These results are compatible with earlier studies that evaluated the use of mepolizumab in severe eosinophilic asthma (9–11). Blood eosinophil count significantly decreased in all treated patients, with a rapid decline in the first month of treatment. We also found a major improvement in QoL. The mean FEV1 modestly increased during the study follow-up period. We have shown similar efficacy to

former clinical trials, in this real-world cohort with a follow-up period of up to 24 months, and with good adherence to therapy. This is of importance since current evidence are mostly from RCTs where the drug is given free of charge and at designated centers. Eligibility for mepolizumab therapy in Israel requires severe uncontrolled asthma with frequent exacerbations despite therapy with high dose inhaled corticosteroids (ICS), and blood eosinophil count of over 400 cells/microL, thus the population evaluated in this trial were patients with severe uncontrolled asthma, similar to earlier studies.

Response time to treatment is of importance since there is no consensus on the timing of drug discontinuation in cases with no clinical response to therapy. In this study, we have shown that the majority of the therapeutic effects occur in the first three months with a statistically significant response to therapy after

6 months. No additional therapeutic effects were seen after 6 months. This is in accordance with patient's QoL interviews; the large majority of patients who reported a good response to therapy, stated they felt a beneficial effect within 3 months (only two patients stated they felt a beneficial effect after 5 months). Moreover, our analysis also showed a sustained and lasting effect after one year of therapy.

Adverse events were mild, and the majority resolved after the first dose. Previous trials have also reported a favorable safety profile with Mepolizumab (12,18,19).

This study has several limitations. First, its small cohort size; nonetheless, the compatibility of our results with the literature and the large effect demonstrated, validate the robustness of the results. Second, we evaluated the quality of life with an unstandardized questionnaire, nevertheless, the large effect size (80% reported an improvement in QoL) reduces the probability of recall bias. Finally, we did not have a control group. However, as mepolizumab is already approved for therapy in Israel for patients with severe asthma, it would be unethical to withhold this treatment. The strengths of the study are its real-world cohort with 2-year follow-up and independent design without external funding. Notably, no pharmaceutical company was involved in this study.

Anti-IL-5 therapy is currently available in multiple countries, and there is a substantial amount of evidence with reports of favorable results (19–23). Mepolizumab was also shown to be an effective treatment for Eosinophilic granulomatosis with polyangiitis (EGPA) in higher doses (300 mg monthly) and for hypereosinophilic syndrome (HES). In both entities treatment with mepolizumab resulted in reduced doses of corticosteroids (24,25). Physicians' awareness to anti IL-5 treatment should be increased, not only among pulmonologists but also among general practitioners, emergency room physicians and within Internal medicine wards.

In conclusion, treatment with mepolizumab was well tolerated and significantly lowered the exacerbation rate and OCS dependence in a real-world cohort of severe eosinophilic asthma patients. Response to therapy was within six months and treatment effect was sustained over time.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References

1. Diagnosis and Management of Difficult-to-treat and Severe Asthma [Internet]. Global Initiative for Asthma - GINA. Available from: <https://ginasthma.org/severeasthma/> [last accessed 23 August 2019].
2. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343–373. doi:10.1183/09031936.00202013.
3. Passalacqua G. Anti-interleukin 5 therapies in severe asthma. *Lancet Respir Med*. 2017;5:537–538. doi:10.1016/S2213-2600(17)30206-0.
4. Dorman SC, Efthimiadis A, Babirad I, Watson RM, Denburg JA, Hargreave FE, O'Byrne PM, Sehmi R. Sputum CD34 + IL-5Ralpha + cells increase after allergen: evidence for. *Am J Respir Crit Care Med*. 2004;169:573–577. doi:10.1164/rccm.200307-1004OC.
5. Wood LJ, Sehmi R, Dorman S, Hamid Q, Tulic MK, Watson RM, Foley R, Wasi P, Denburg JA, Gauvreau G, et al. Allergen-induced increases in bone marrow T lymphocytes and interleukin-5 expression in subjects with asthma. *Am J Respir Crit Care Med*. 2002;166:883–889. doi:10.1164/rccm.2108015.
6. Pelaia C, Vatrella A, Busceti MT, Gallelli L, Terracciano R, Savino R, Pelaia G. Severe eosinophilic asthma: from the pathogenic role of interleukin-5 to the therapeutic action of mepolizumab. *DDDT* 2017; 11:3137–3144. doi:10.2147/DDDT.S150656.
7. Lopez AF, Begley CG, Williamson DJ, Warren DJ, Vadas MA, Sanderson CJ. Murine eosinophil differentiation factor. An eosinophil-specific colony-stimulating factor with activity for human cells. *J Exp Med*. 1986;163:1085–1099. doi:10.1084/jem.163.5.1085.
8. Chung KF. Targeting the interleukin pathway in the treatment of asthma. *Lancet* 2015;386:1086–1096. doi:10.1016/S0140-6736(15)00157-9.
9. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360:973–984. doi:10.1056/NEJMoa0808991.
10. Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, Hargreave FE, O'Byrne PM. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med*. 2009;360:985–993. doi:10.1056/NEJMoa0805435.
11. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet Lond Engl*. 2012; 380:651–659. doi:10.1016/S0140-6736(12)60988-X.
12. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017;9:CD010834. Available from: doi:10.1002/14651858.CD010834.pub3.

13. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, Ferguson GT, Busse WW, Barker P, Sproule S, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Lond Engl*. 2016; 388:2128–2141. doi:[10.1016/S0140-6736\(16\)31322-8](https://doi.org/10.1016/S0140-6736(16)31322-8).
14. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, Gilmartin G, Aurivillius M, Werkström V, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet Lond Engl*. 2016;388:2115–2127. doi:[10.1016/S0140-6736\(16\)31324-1](https://doi.org/10.1016/S0140-6736(16)31324-1).
15. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C, Korn S, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3:355–366. doi:[10.1016/S2213-2600\(15\)00042-9](https://doi.org/10.1016/S2213-2600(15)00042-9).
16. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest* 2016;150:789–798. doi:[10.1016/j.chest.2016.03.032](https://doi.org/10.1016/j.chest.2016.03.032).
17. Castro M, Mathur S, Hargreave F, Boulet L-P, Xie F, Young J, Wilkins HJ, Henkel T, Nair P. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2011;184:1125–1132. doi:[10.1164/rccm.201103-0396OC](https://doi.org/10.1164/rccm.201103-0396OC).
18. Roufosse FE, Kahn J-E, Gleich GJ, Schwartz LB, Singh AD, Rosenwasser LJ, Denburg JA, Ring J, Rothenberg ME, Sheikh J, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol*. 2013;131:461–467.e1–5. doi:[10.1016/j.jaci.2012.07.055](https://doi.org/10.1016/j.jaci.2012.07.055).
19. Lugogo N, Domingo C, Chanez P, Leigh R, Gilson MJ, Price RG, Yancey SW, Ortega HG. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther*. 2016;38:2058–2070.e1. doi:[10.1016/j.clinthera.2016.07.010](https://doi.org/10.1016/j.clinthera.2016.07.010).
20. Bagnasco D, Caminati M, Ferrando M, Aloè T, Testino E, Canonica GW, Passalacqua G. Anti-IL-5 and IL-5Ra: efficacy and safety of new therapeutic strategies in severe uncontrolled asthma. *BioMed Res Int*. 2018;2018:1. doi:[10.1155/2018/5698212](https://doi.org/10.1155/2018/5698212).
21. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, Barros M, Buhl R, Howarth P, Albers FC, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol*. 2019;143:1742–1751.e7. doi:[10.1016/j.jaci.2018.09.033](https://doi.org/10.1016/j.jaci.2018.09.033).
22. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, Sproule S, Olsson RF, Martin UJ, Goldman M, Yañez A, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med*. 2019;7: 46–59. doi:[10.1016/S2213-2600\(18\)30406-5](https://doi.org/10.1016/S2213-2600(18)30406-5).
23. Murphy K, Jacobs J, Bjermer L, Fahrenholz JM, Shalit Y, Garin M, Zangrilli J, Castro M. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract*. 2017;5: 1572–1581.e3. doi:[10.1016/j.jaip.2017.08.024](https://doi.org/10.1016/j.jaip.2017.08.024).
24. Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon H-U, Schwartz LB, Rosenwasser LJ, Ring J, Griffin EF, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med*. 2008;358:1215–1228. doi:[10.1056/NEJMoa070812](https://doi.org/10.1056/NEJMoa070812).
25. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, Merkel PA, Moosig F, Specks U, Cid MC, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med*. 2017; 376:1921–1932. doi:[10.1056/NEJMoa1702079](https://doi.org/10.1056/NEJMoa1702079).