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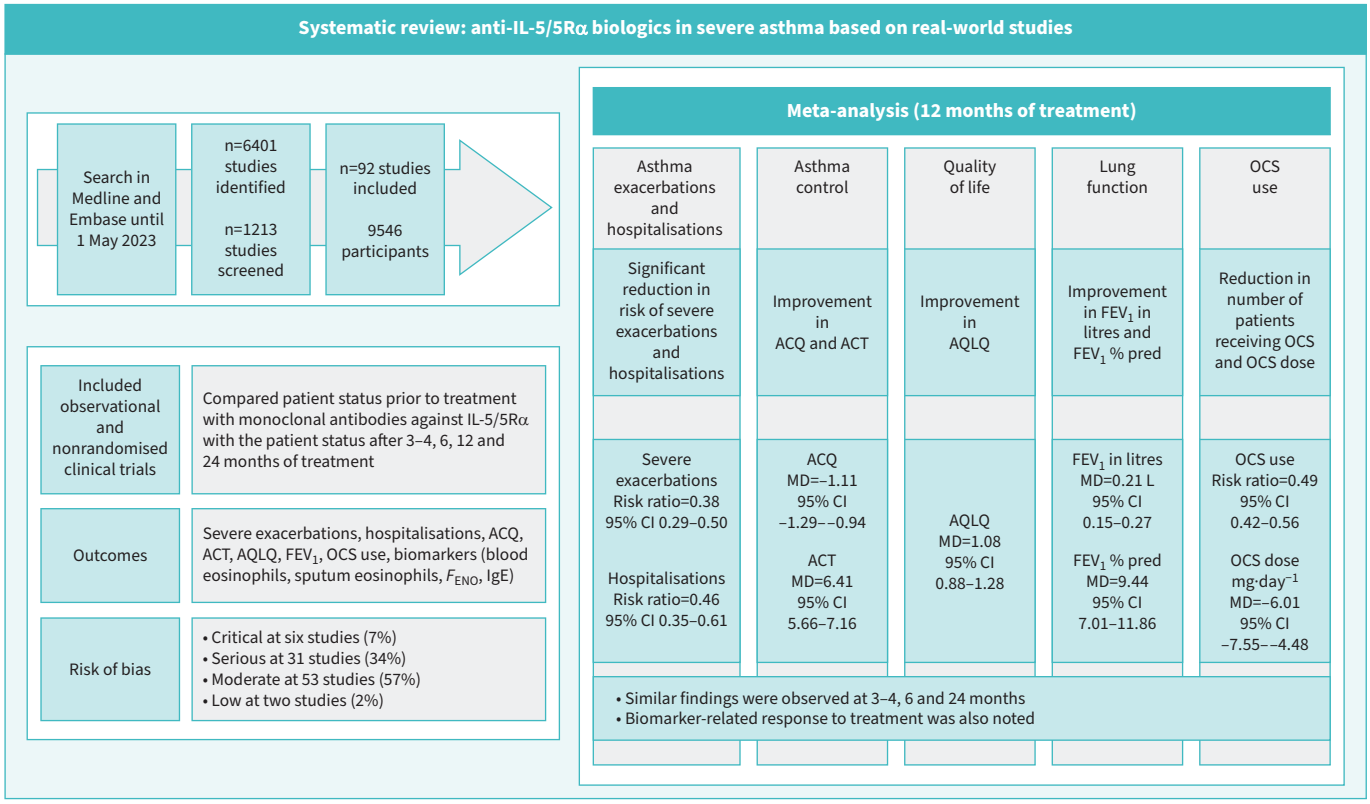

GRAPHICAL ABSTRACT ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; FEV_1: forced expiratory volume in 1 s; F_{ENO}: exhaled nitric oxide fraction; IL: interleukin; MD: mean difference; OCS: oral corticosteroid; R: receptor.

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Christos Kyriakopoulos [1], Efthymia Papadopoulou [2], Dimitrios Potonos[1], Konstantinos Exarchos [1], Evangelos Beris[1], Christina Aggelopoulou[1], Stavros Tryfon [2], Athena Gogali[1] and Konstantinos Kostikas [1]

[1]Respiratory Medicine Department, Faculty of Medicine, University of Ioannina, Ioannina, Greece. [2]Respiratory Medicine Department, General Hospital of Thessaloniki G Papanikolaou, Thessaloniki, Greece.

Corresponding author: Konstantinos Kostikas (ktkostikas@gmail.com)

Shareable abstract (@ERSpublications)
Anti-IL-5/5Rα biologics reduced severe exacerbations and hospitalisations, improved asthma control, quality of life and lung function, and decreased systemic corticosteroids use in real-life settings; a biomarker-related response to treatment was also noted https://bit.ly/3MW4JR3

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Abstract

Background Three biologics targeting interleukin 5 (anti-IL-5) or its receptor-α (anti-IL-5Rα) are approved for patients with severe asthma.

Methods We systematically searched the literature published in Medline and Embase up to 1 May 2023 to identify observational studies and nonrandomised trials that assess the response to anti-IL-5/5Rα in real-life patients with severe eosinophilic asthma. We also performed random-effects meta-analyses.

Results We identified 6401 studies, of which 92 with 9546 patients were analysed. Biologics use was associated with a 62% reduction in severe exacerbations (risk ratio 0.38, 95% CI 0.29–0.50) and a 54% reduction in hospitalisations (risk ratio 0.46, 95% CI 0.35–0.61) at 12 months of treatment, compared to pre-treatment. Biologics improved asthma control (decrease in asthma control questionnaire score by 1.11 points (95% CI −1.29–−0.94) and increase in asthma control test score by 6.41 points (95% CI 5.66–7.16)) and increased the asthma quality of life questionnaire score by 1.08 points (95% CI 0.88–1.28) and forced expiratory volume in 1 s by 0.21 L (95% CI 0.15–0.27) at 12 months. There was a significant reduction in oral corticosteroids use of 51% (risk ratio 0.49, 95% CI 0.42–0.56), with a mean dose reduction of 6.01 mg·day^{-1} (95% CI −7.55–−4.48) at 12 months of treatment. Similar findings were observed at 3–4, 6 and 24 months. A biomarker-related response to treatment was also noted.

Conclusions This comprehensive meta-analysis summarises the significant clinical response to anti-IL-5/5Rα biologics in real-life studies, providing important insights for their use in clinical practice.

Introduction

Asthma is a heterogeneous disease affecting more than 300 million patients worldwide [1]. The course of asthma is defined by three parameters, namely asthma control, asthma severity and exacerbations. Asthma control is assessed by symptoms, activities of daily living and quality of life, severity describes the difficulty in controlling asthma with treatment, reflecting the level of treatment required, and exacerbations are episodes of worsening of symptoms that call for additional treatment. Recurrent asthma exacerbations remain a major unmet need in asthma treatment, leading to a high personal and social impact as well as substantial healthcare costs.

Severe asthma constitutes a small (3–10% of adult asthma population) but problematic entity [2], representing asthma that remains uncontrolled despite maximal optimised therapy and treatment of contributory factors, or that worsens when high-dose treatment is decreased [3]. Advances in understanding the pathophysiology of eosinophilic inflammation has led to the identification of biomarkers and the approval of biologics for the treatment of severe asthma, targeting interleukin 5 (anti-IL-5, mepolizumab [4, 5] and reslizumab [6, 7]) and its α-receptor (anti-IL-5Rα, benralizumab [8, 9]).

Observational studies and nonrandomised clinical trials are designed to complement the findings of randomised controlled trials (RCTs) in wider populations and/or for longer follow-up periods. Moreover, many severe asthma patients have characteristics that make them ineligible for inclusion in RCTs, including comorbidities, low bronchodilator reversibility, persistent airflow limitation or a smoking habit. The existing observational studies of anti-IL-5/5Rα biologics usually involve small patient numbers, rendering a meta-analysis of nonrandomised studies (NRS) important to assess the effectiveness of these medicines in this broader population.

In this systematic review and meta-analysis we assess the early and long-term effectiveness of anti-IL-5/5Rα monoclonal antibodies on clinically relevant and biomarker-related outcomes in real-life studies of patients with severe eosinophilic asthma.

Methods

This systematic review and meta-analysis follows a pre-registered protocol in the OSF Registry (https://doi.org/10.17605/OSF.IO/A8YMW) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [10] reporting guidelines (supplementary appendix 1).

Literature search and inclusion criteria

We conducted a systematic literature search of Medline (PubMed) and Embase from inception until 1 May 2023 to identify NRS and observational studies that assess the response to anti-IL-5/5Rα in real-life patients with severe or uncontrolled eosinophilic asthma. The searches were carried out independently by

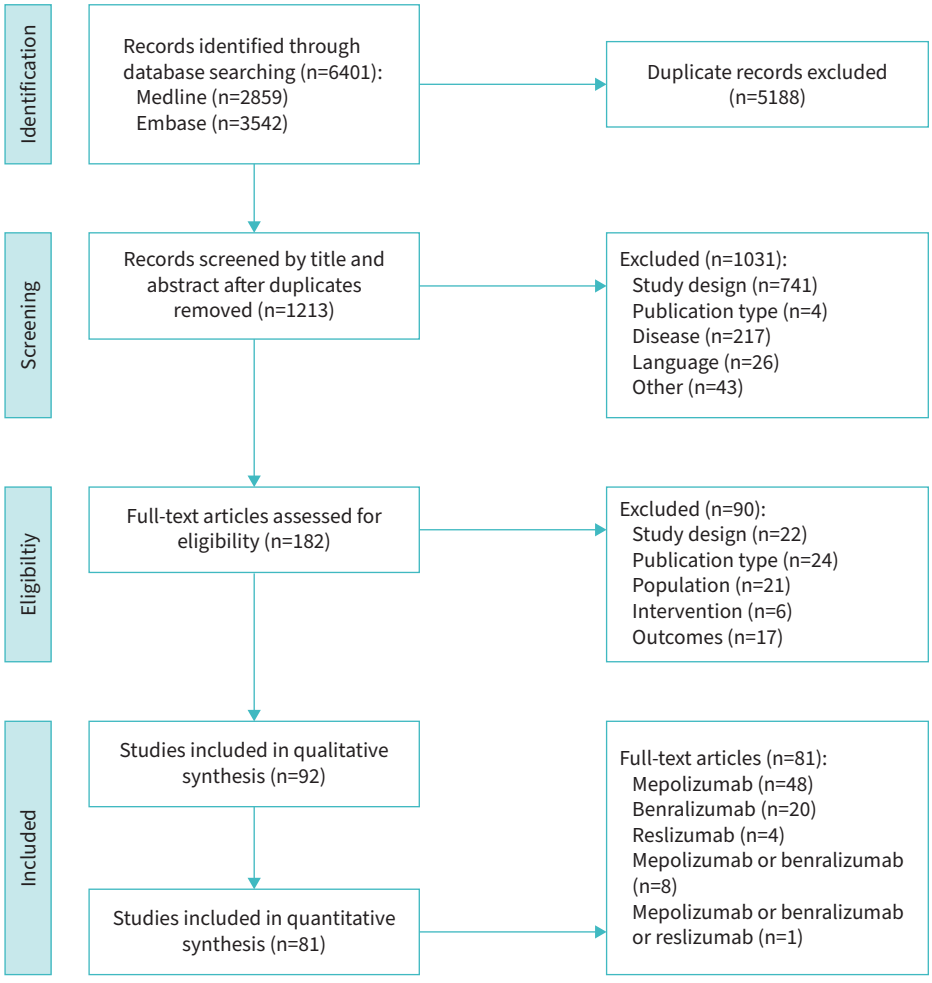

FIGURE 1 Systematic review and meta-analysis flow-diagram illustrating the systematic search and screening strategy, including number of studies meeting eligibility criteria and number of excluded studies.

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TABLE 1 Study characteristics of 92 studies that met eligibility criteria for assessment of biologic agents against interleukin (IL-) 5 (mepolizumab and reslizumab) and its receptor α (benralizumab) for eosinophilic asthma

First author, year, reference	Duration	Number of participants	Biologic agent	Study design	Age (years)[#]	Never-smokers (%)	Asthma duration (years)[#]	OCS mean daily dose prior to anti-IL-5 treatment (mg)[#]
AlShareef 2022 [13]	12 months	35	Mepolizumab	Retrospective observational	49.9	23 (65.7)	–	–
Antonicelli 2020 [14]	6 months	18	Mepolizumab	Prospective observational	54.5±9.1	8 (44.4)	19.1±9.5	5.0±5.7
Atayik 2022 [15]	12 months	57	Mepolizumab	Retrospective observational	45.1±14.7	–	10 (2–30)	4 (0–16)
Bagnasco 2020 [16]	12 months	138	Mepolizumab	Retrospective observational	58±10	–	24±12	10.1±9.4
Bagnasco 2020 [17]	6 months	59	Benralizumab	Retrospective observational	53 (32–78)	–	–	12.0±8.1
Benjamin 2018 [18]	6 months	28	Mepolizumab	Retrospective observational	50.9±10.0	18 (64.3)	–	9.6±3.6
Bjerrum 2021 [19]	24 months	81	Mepolizumab/benralizumab/ reslizumab	Retrospective observational	55	–	–	10 (5–20)
Brás 2021 [20]	12 months	20	Mepolizumab	Retrospective observational	54.0±17.0	18 (90)	22.0±16.0	10.2
Buonamico 2020 [21]	6 months	10	Benralizumab	Prospective observational	48.9±10.1	–	–	–
Cameli 2020 [22]	6 months	26	Mepolizumab	Retrospective observational	56.4±11.7	11 (42.3)	19.9±12.2	3.0±4.8
Carpagnano 2019 [23][¶]	12 months	4	Mepolizumab	Prospective observational	55±9	4 (100)	–	0
Carpagnano 2020 [24][¶]	12 months	41	Mepolizumab	Retrospective observational	56.8±9	26 (63.4)	22.1±9.3	–
Chan 2022 [25][+]	24 weeks	21	Benralizumab	Non–randomized clinical trial	53±4	13 (61.9)	–	–
Chitguppi 2020 [26]	4 months	23	Benralizumab	Retrospective observational	50.5±17.3	18 (78.2)	–	–
Chung 2022 [27]	12 months	204	Benralizumab	Retrospective observational	45.3±16.6	–	–	30.6±11.7
Contoli 2022 [28]	4 months	186	Mepolizumab	Retrospective observational	57	54 (29.1)	–	–
Crimi 2021 [29]	12 months	32	Mepolizumab	Retrospective observational	52.3±10	–	19.5±12.5	8.8 (0–25)
d'Ancona 2020 [30]	12 months	91	Mepolizumab	Retrospective observational	53.7±14.4	63 (69.2)	–	10 (10–15)
d'Ancona 2021 [31]	12 months	89	Benralizumab	Retrospective observational	52.7±14.8	65 (73)	–	12.4±9.4
Detoraki 2021 [32]	12 months	44	Mepolizumab	Prospective observational	54±12	28 (63.6)	–	8.6±11.2
Dhariwal 2021 [33]	12 months	153	Mepolizumab/benralizumab	Retrospective observational	54.2	–	–	10
Di Bona 2020 [34]	6 months	15	Benralizumab	Retrospective observational	55.2±14	15 (100)	9.6±5.7	15
Domingo 2021 [35]	12 months	318	Mepolizumab	Retrospective observational	56.6±12.5	198 (62.2)	–	12.1±10
Drick 2018 [36]	12 months	32	Mepolizumab	Retrospective observational	51 (44–60)	–	–	5 (5–10)
Drick 2022 [37]	6 months	42	Mepolizumab/benralizumab	Retrospective observational	61 (55–66)	28 (66.7)	–	10 (5–20)
Eldaboussi 2021 [38]	12 months	63	Benralizumab	Retrospective observational	47.4	–	–	6
Enríquez–Rodríguez 2021 [39]	12 months	69	Mepolizumab	Retrospective observational	56±13		–	18±14.2
Farah 2019 [40]	6 months	20	Mepolizumab	Prospective observational	60±16	16 (80)	–	–
Fong 2021 [41]	12 months	62	Mepolizumab	Retrospective observational	61±19	27 (43.5)	33	10±5
Gallo 2022 [42]	12 months	43	Mepolizumab	Retrospective observational	52.2±10.9	27 (62.8)	–	–
González–Pérez 2022 [43]	52 weeks	61	Mepolizumab	Retrospective observational	46±39	41 (67.2)	–	11.3±9.6
Harvey 2020 [44]	12 months	309	Mepolizumab	Prospective observational	59.6 (49.9–68.3)	186 (60.2)	27.5 (13.3–46.1)	10 (5.0–12.5)
Hashimoto 2022 [45]	12 months	134	Reslizumab	Retrospective observational	53.4	77 (57.5)	–	5 (0–10)
Ibrahim 2019 [46]	24 months	26	Reslizumab	Non–randomized clinical trial	52±13.5	–	–	9.3±4.3
Isoyama 2021 [47]	24 weeks	20	Mepolizumab	Retrospective observational	77.5±1.3	9 (45)	19.5±4.2	14.6±3.3
Izumo 2020 [48]	12 weeks	26	Benralizumab	Non–randomized clinical trial	66.8 (60.9–72.8)	18 (69.2)	–	4.1 (1.6–6.5)
Jackson 2022 [49]	48 weeks	208	Benralizumab	Retrospective observational	50.5±14.5	–	–	13.9±12.1
Kallieri 2020 [50][¶]	12 months	70	Mepolizumab	Prospective observational	55±12	59 (84.3)	20±13	10.1±7
Kallieri 2022 [51][¶]	24 months	169	Mepolizumab	Prospective observational	57.7±12.6	109 (64.5)	21.1 (9.0–30.0)	10.6±7.5
Kavanagh 2020 [52]	12 months	99	Mepolizumab	Retrospective observational	53.5±13.2	53 (53.5)	–	10 (10–15)

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TABLE 1 Continued

First author, year, reference	Duration	Number of participants	Biologic agent	Study design	Age (years)[#]	Never-smokers (%)	Asthma duration (years)[#]	OCS mean daily dose prior to anti-IL-5 treatment (mg)[#]
Kavanagh 2021 [53]	48 weeks	130	Benralizumab	Retrospective observational	52.8±14.0	88 (67.7)	–	10 (5–20)
Kayser 2021 [54]	12 months	187	Mepolizumab/benralizumab	Retrospective observational	58	100 (53.4)	–	7.69
Kimura 2021 [55]	12 months	151	Mepolizumab/benralizumab	Retrospective observational	52.3	–	–	2.66
Koistinen 2022 [56]	24 months	51	Mepolizumab	Retrospective observational	54.8±12.2	31 (60.8)	16.2±16.5	9.8±5.6
Koya 2020 [57]	12 months	3	Mepolizumab	Prospective observational	59.3±9.2	1 (33.3)	14±4.6	5.8±5.2
Kroes 2022 [58]+	52 weeks	22	Mepolizumab	Prospective observational	52 (46–61)	12 (54.5)	–	8.8 (2.5–10)
Kurosawa 2019 [59]	48 weeks	32	Mepolizumab	Prospective observational	63	–	17.5	–
Llanos 2020 [60]	12 months	346	Mepolizumab	Retrospective observational	49.3±12.0	–	–	–
Maglio 2021 [61]	18 months	105	Mepolizumab	Retrospective observational	58.5±11	58 (55.2)	21.5±13.7	–
Martínez–Moragón 2021 [62]	9 months	27	Benralizumab	Retrospective observational	49.8±12.7	19 (70.4)	19.2±13.8	20.3±20.1
Matsuno 2020 [63]+	12 months	17	Benralizumab	Retrospective observational	63.7	8 (47.1)	24	8.6
Matucci 2022 [64]	36 months	51	Mepolizumab	Retrospective observational	57±9.5	–	–	7.3±4.3
Maza–Solano 2022 [65]+	4 months	38	Mepolizumab	Prospective observational	56.7±9	22 (57.9)	–	–
McDowell 2022 [66]	12 months	101	Mepolizumab	Prospective observational	54.4±11.9	60 (59.4)	–	10 (10–15)
Menigoz 2022 [67]	12 months	110	Mepolizumab/benralizumab	Retrospective observational	63 (49–65)	68 (61.9)	–	15.8±12.1
Menzella 2021 [68]	12 months	115	Mepolizumab/benralizumab	Retrospective observational	57.2	73 (63.5)	–	4.9
Menzella 2022 [69]+	48 weeks	205	Benralizumab	Retrospective observational	55.8±13.3	139 (67.8)	12.4 (6.3–24.6)	10 (5–25)
Menzies-Gow 2022 [70]	12 months	598	Benralizumab	Non–randomized clinical trial	53.3±13.6	446 (74.6)	–	10
Miralles López 2022 [71]	12 months	84	Benralizumab	Retrospective observational	59.5	43 (51.2)	23	10 (5–20)
Mümmler 2021 [72]+	6 months	26	Mepolizumab/benralizumab	Retrospective observational	60±13.1	15 (57.7)	–	5
Nagase 2021 [73]	12 months	61	Mepolizumab	Retrospective observational	52.9	–	–	8 (7–11)
Nolasco 2021 [74]	24 weeks	137	Benralizumab	Retrospective observational	53.9±13.5	104 (75.9)	–	10 (5–25)
Nowak–Jurek 2022 [75]+	24 weeks	12	Mepolizumab	Prospective observational	55	–	–	0 (0–5)
Numata 2019 [76]	11 months	27	Mepolizumab	Retrospective observational	56.3±11.8	20 (74.1)	19.6±11.9	8.4±5.6
Numata 2022 [77]	38 months	23	Benralizumab	Retrospective observational	59.8±10.3	15 (65.2)	21.9±12.7	6 (2.5–15)
Ortega 2020 [78]	12 months	201	Mepolizumab	Retrospective observational	55.9±13.7	–	–	–
Özdel Öztürk 2021 [79]	12 months	62	Mepolizumab	Retrospective observational	44.4±13.2	–	7 (1–35)	8 (2–40)
Padilla-Galo 2021 [80]	12 months	44	Benralizumab	Prospective observational	53.8±10.4	23 (52.3)	–	19.3±8.8
Pelaia 2020 [81]	12 months	88	Mepolizumab	Retrospective observational	54.5±10.8	–	20 (10–30)	6.25 (0–25)
Pelaia 2021 [82]	6 months	111	Benralizumab	Retrospective observational	56 (43–65)	79 (71.2)	18 (10–30)	5 (0–12.5)
Pérez de Llano 2022 [83]	12 months	208	Reslizumab	Retrospective observational	56.4±11.3	145 (69.7)	–	5.6 (3–13.5)
Pertzov 2021 [84]	3 months	61	Mepolizumab	Prospective observational	57.5±13.2	–	–	20 (6.2–40)
Pilette 2022 [85]	12 months	822	Mepolizumab	Prospective observational	54±13.6	489 (59.5)	19.7	10 (5–15)
Pini 2021 [86]	12 months	87	Mepolizumab	Prospective observational	56±10.8	55 (63.2)	–	9.9±7.6
Renner 2020 [87]+	20 weeks	35	Mepolizumab	Prospective observational	57.4 (40–80)	11 (31.4)	16.5	6.25 (0–20)
Renner 2020 [88]+	48 weeks	56	Benralizumab	Retrospective observational	60±5.3	31 (55.3)	–	5.6 (5–22.5)
Rial 2021 [89]+	8 weeks	16	Mepolizumab/reslizumab	Prospective observational	58±13	10 (62.5)	–	–
Rodríguez–García 2021 [90]	6 months	122	Mepolizumab	Retrospective observational	58.4±12.7	96 (78.7)	–	7.1±7.3
Schleich 2020 [91]	30 months	116	Mepolizumab	Prospective observational	54±14	74 (63.8)	–	8 (7–12)
Scioscia 2021 [92]	24 weeks	10	Benralizumab	Prospective observational	54±8.8	9 (90)	–	–
Shirai 2020 [93]+	24 weeks	22	Benralizumab	Prospective observational	55 (28–82)	15 (68.2)	27 (2–47)	3.9–13.3
Silver 2020 [94]	12 months	527	Mepolizumab	Retrospective observational	49.4±11.9	–	–	6.7±7.8

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TABLE 1 Continued

First author, year, reference	Duration	Number of participants	Biologic agent	Study design	Age (years)[#]	Never-smokers (%)	Asthma duration (years)[#]	OCS mean daily dose prior to anti-IL-5 treatment (mg)[#]
Sposato 2020 [95]	10.9 months	134	Mepolizumab	Retrospective observational	58.3±11	85 (63.4)	–	–
Sposato 2022 [96]	19.7 months	95	Benralizumab	Retrospective observational	58.1±12.2	64 (67.4)	–	14.8±8.9
Strauss 2018 [97]	12 months	36	Mepolizumab	Retrospective observational	58 (36–92)	25 (69.4)	33 (2.5–61)	7–60
Taillé 2020 [98]	24 months	146	Mepolizumab	Retrospective observational	58.2±13.6	77 (52.7)	13.4±12.1	20.6±16.5
Thomas 2021 [99]	12 months	300	Mepolizumab	Prospective observational	59.6 (49.8-68.2)	182 (60.7)	27.5 (13.5-46.1)	10 (5–12.5)
Tiotiu 2022 [100]	6 months	37	Mepolizumab/benralizumab	Retrospective observational	54	29 (78.4)	–	–
van Toor 2021 [101]	12 months	78	Mepolizumab	Retrospective observational	54 (20–83)	51 (65.4)	–	10 (3–50)
Vantaggiato 2022 [102]	6 months	18	Mepolizumab/benralizumab	Prospective observational	53.5	6 (33.3)	–	3.8
Voelker 2020 [103]	24 months	63	Mepolizumab	Retrospective observational	54.2	45 (71.4)	–	15
Wechsler 2021 [104]	12 months	215	Reslizumab	Retrospective observational	45.2±11.9	174 (80.9)	–	–
Yamada 2021 [105]	4 months	64	Benralizumab	Retrospective observational	69.4±12.5	32 (50)	–	–
Yilmaz 2021 [106]	12 months	41	Mepolizumab	Retrospective observational	48.8±10.6	39 (95.1)	11.2±5.8	5 (0–20)

[#]: Values are presented as mean±SD or median (interquartile range). [¶]: Carpagnano 2019 [23] and Kallieri 2020 [50] are previous reports of the studies Carpagnano 2020 [24] and Kallieri 2022 [51], respectively. Outcomes not reported in the final reports, were extracted from the initial reports. [+]: Included only in the qualitative analysis, due to lack of documentation of statistical measures or skewed data. OCS: oral corticosteroid.

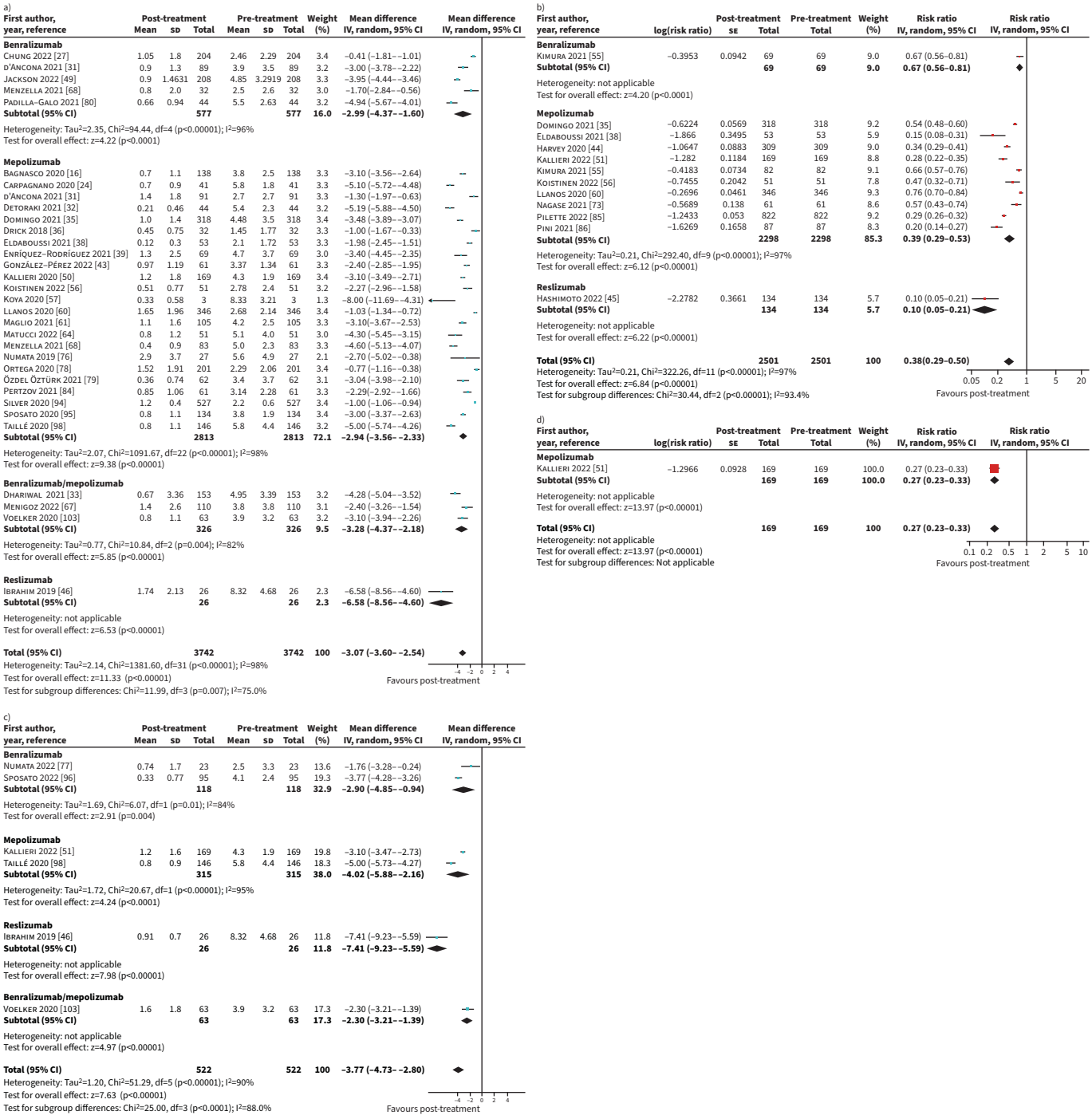


FIGURE 2 a) Forest plot of the mean change in the annual rate of asthma severe exacerbations after 12 months of anti-interleukin (IL)-5/5Rα treatment compared to pre-treatment. b) Forest plot of asthma severe exacerbations relative risk after 12 months of anti-IL-5/5Rα treatment compared to pre-treatment. c) Forest plot of the mean change in the annual rate of asthma severe exacerbations after 24 months of anti-IL-5/5Rα treatment compared to pre-treatment. d) Forest plot of asthma severe exacerbations relative risk after 24 months of anti-IL-5/5Rα treatment compared to pre-treatment. In all panels, sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. IV: inverse variance.

three reviewers (C.K., E.B. and A.G.) in a standardised manner, followed by screening through relevant titles and abstracts, before full-text review. Disagreements were resolved by consensus, with unresolved conflicts decided by a fourth reviewer (K.K.) (supplementary appendix 2). In studies where other

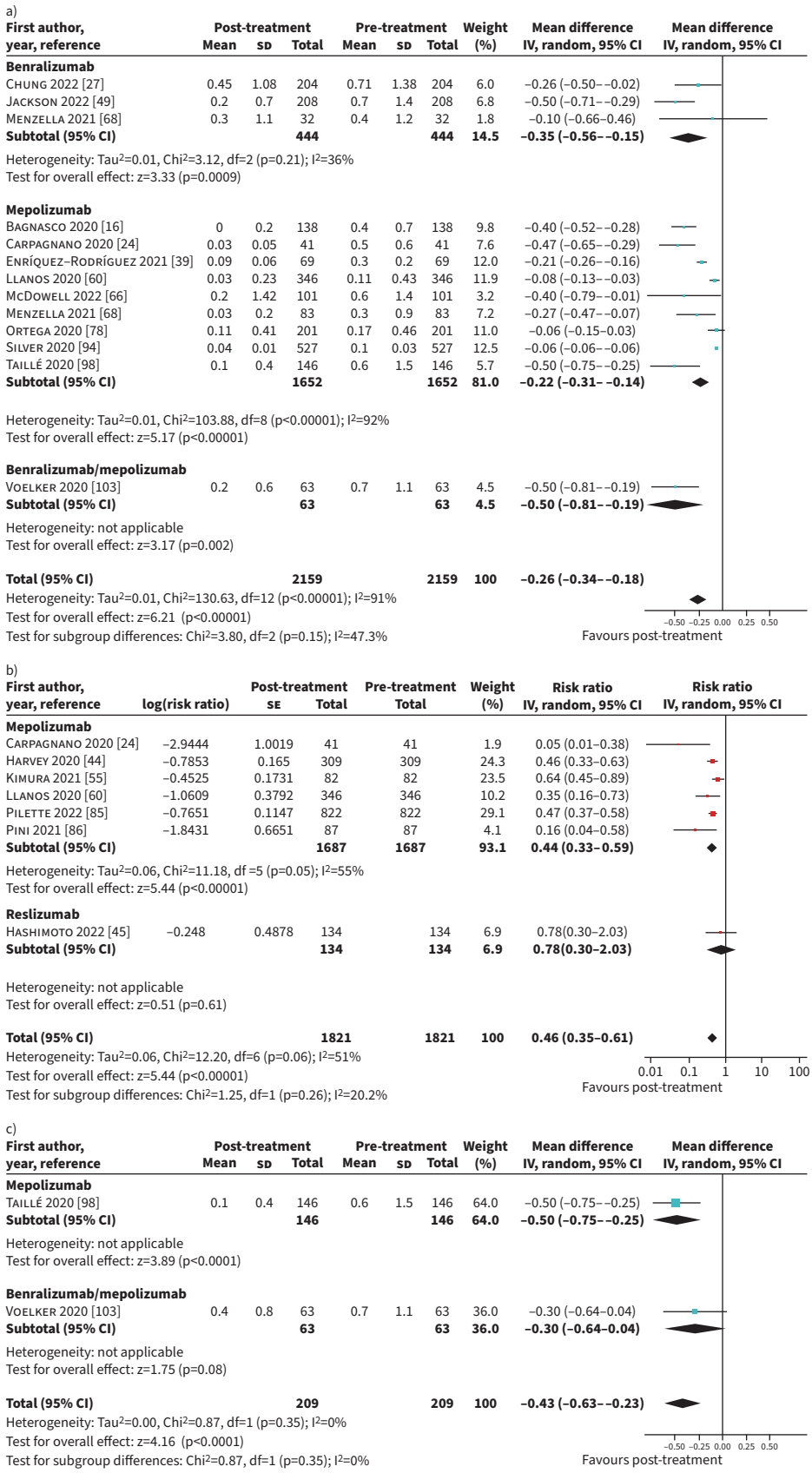


FIGURE 3 a) Forest plot of the mean change in the annual rate of hospitalisations due to asthma exacerbation after 12 months of anti-interleukin (IL)-5/5Rα treatment compared to pre-treatment. b) Forest plot of

hospitalisations due to asthma exacerbation relative risk after 12 months of anti-IL-5/5Rα treatment compared to pre-treatment. c) Forest plot of the mean change in the annual rate of hospitalisations due to asthma exacerbation after 24 months of anti-IL-5/5Rα treatment compared to pre-treatment. In all panels, sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. IV: inverse variance.

monoclonal antibodies, such as omalizumab (monoclonal antibody against immunoglobulin E), dupilumab (monoclonal antibody against IL-4 receptor-α) or tezepelumab (monoclonal antibody against thymic stromal lymphopoetin), were used in severe asthma therapy as well, only data pertaining to anti-IL-5/5Rα antibodies were extracted. Eligible studies met the following criteria based on the participants–intervention–comparator–outcome–time-frame (PICOT) format.

Participants

Nonrandomised, observational and uncontrolled before–after studies, evaluating patients >18 years old with moderate-to-severe, severe, uncontrolled and inadequately controlled eosinophilic asthma.

Intervention

Monoclonal antibodies against IL-5 (anti-IL-5, mepolizumab and reslizumab) and its receptor α (anti-IL-5Rα, benralizumab).

Comparator group

Patient status prior to treatment initiation with monoclonal antibodies against IL-5/5Rα.

Outcomes

Primary end-point: severe exacerbations (annual rate).

Secondary end-points: 1) hospitalisations for asthma exacerbation (annual rate), 2) asthma control questionnaire (ACQ) and asthma control test (ACT), 3) asthma quality of life questionnaire (AQLQ), 4) lung function (forced expiratory volume in 1 s (FEV_1) in litres and FEV_1 % pred), 5) oral corticosteroids (OCS) use (number of patients and daily dose) and sparing effect (reduction to <5 mg prednisolone·day^{-1}), 6) biomarkers (blood eosinophils, sputum eosinophils (%), fractional exhaled nitric oxide (F_{ENO}) and IgE).

Time-frame

Without limitation in the follow-up duration of the included studies.

Severe exacerbations and hospitalisations were analysed at 12 and 24 months of treatment, while ACQ, ACT, AQLQ, FEV_1 (L), FEV_1% pred, OCS use and sparing effect, blood eosinophils, sputum eosinophils, F_{ENO} and IgE were assessed at 3–4, 6, 12 and 24 months, when data were available. These time-points were adopted since they allow the assessment of early response (3–4 months), maximum response (6 months) and the maintenance of biologics effects (12 and 24 months).

Data extraction and risk of bias assessment

Two authors (E.B. and C.A.) concurrently reviewed all eligible studies to perform data extraction. The reviewers worked independently during the extraction of study data; disagreements, if any, were resolved by discussion to obtain consensus, with unresolved conflicts decided by a third reviewer (C.K.). Obtained data were validated by a third independent author (D.P.). From each eligible study, we recorded information about the first author, publication year, journal, study design, follow-up time, population characteristics, treatment indication and biological agent. In addition to the number of patients, we extracted risk ratios with confidence intervals for dichotomous data and means with standard deviations or medians with interquartile ranges, along with mean changes from baseline and confidence intervals for continuous data. The risk of bias of eligible trials was assessed at study level by using the Risk Of Bias In Non-Randomised Studies of Interventions (ROBINS-I) tool (supplementary appendix 6) [11].

Data analysis

We performed random-effects meta-analysis (Review Manager 5.4.1, Cochrane) to account for the significant clinical and methodological heterogeneity. Dichotomous and continuous outcomes were described with relative risks and mean differences (MDs), respectively, along with their 95% confidence intervals. Heterogeneity was assessed with the I^2 statistic (ranging from 0% to 100%) [12]. We assessed all

a)

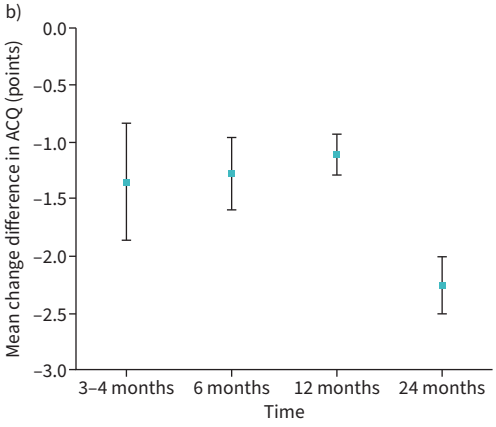
First author, year, reference	Post-treatment Mean	SD	Total	Pre-treatment Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Benralizumab								
d'Ancona 2021 [31]	2.08	1.43	89	2.94	1.42	89	5.2	−0.86 (−1.28−−0.44)
Jackson 2022 [49]	2.1	1.9	208	3.025	1.4997	208	5.8	−0.92 (−1.25−−0.60)
Kavanagh 2021 [53]	2.15	1.41	130	2.9	1.39	130	5.7	−0.75 (−1.09−−0.41)
Menzella 2021 [68]	1.1	1.4	32	3.4	0.7	32	4.3	−2.30 (−2.84−−1.76)
Menzies-Gow 2022 [70]	1.25	1.1	598	2.22	1.2	598	6.9	−0.97 (−1.10−−0.84)
Subtotal (95% CI)			**1057**			**1057**	**27.9**	**−1.11 (−1.46−−0.75)**
Heterogeneity: Tau²=0.13, Chi²=24.93, df=4 (p<0.0001); I²=84%								
Test for overall effect: z=6.17 (p<0.00001)								
Mepolizumab								
Carpagnano 2020 [24]	1.6	0.6	41	3.3	0.3	41	6.6	−1.70 (−1.91−−1.49)
d'Ancona 2021 [31]	2.06	1.31	91	2.69	1.33	91	5.4	−0.63 (−1.01−−0.25)
Fong 2021 [41]	1.95	1.64	62	2.71	1.26	62	4.5	−0.76 (−1.27−−0.25)
Kavanagh 2020 [52]	2.2	1.42	99	2.73	1.27	99	5.5	−0.53 (−0.91−−0.15)
Matucci 2022 [64]	0.6	0.9	51	2.6	1.3	51	5.0	−2.00 (−2.43−−1.57)
McDowell 2022 [66]	1.7	1.2	101	2.6	1.3	101	5.7	−0.90 (−1.25−−0.55)
Menzella 2021 [68]	2.3	0.9	83	3.6	0.6	83	6.4	−1.30 (−1.53−−1.07)
Pilette 2022 [85]	1.64	1.68	822	2.87	1.3146	822	6.9	−1.23 (−1.38−−1.08)
Schleich 2020 [91]	2.04	1.2	116	3.09	1.32	116	5.8	−1.05 (−1.37−−0.73)
van Toor 2021 [101]	1.76	1.6	78	2.56	0.96	78	5.2	−0.80 (−1.21−−0.39)
Subtotal (95% CI)			**1544**			**1544**	**57.0**	**−1.11 (−1.36−−0.85)**
Heterogeneity: Tau²=0.14, Chi²=67.33, df=9 (p<0.00001); I²=87%								
Test for overall effect: z=8.53 (p<0.00001)								
Benralizumab/mepolizumab								
Dhariwal 2021 [33]	2	1.37	153	2.82	1.36	153	5.9	−0.82 (−1.31−−0.51)
Menigoz 2022 [67]	1.7	1.3	110	2.8	1.3	110	5.7	−1.10 (−1.44−−0.76)
Subtotal (95% CI)			**263**			**263**	**11.6**	**−0.95(−1.22−−0.68)**
Heterogeneity: Tau²=0.01, Chi²=1.42, df=1 (p=0.23); I²=30%								
Test for overall effect: z=6.80 (p<0.00001)								
Reslizumab								
Ibrahim 2019 [46]	1.7	1.4	26	3.5	1.1	26	3.5	−1.80 (−2.48−−1.12)
Subtotal (95% CI)			**26**			**26**	**3.5**	**−1.80 (−2.48−−1.12)**
Heterogeneity: Not applicable								
Test for overall effect: z=5.16 (p<0.00001)								
Total (95% CI)			**2890**			**2890**	**100**	**−0.11 (−1.29−−0.94)**
Heterogeneity: Tau²=0.11, Chi²=110.74, df=17 (p<0.00001); I²=85%								
Test for overall effect: z=12.25 (p<0.00001)								
Test for subgroup differences: Chi²=5.18, df=3 (p=0.16); I²=42.1%								

Mean difference IV, random, 95% CI

−4 −2 0 2 4

Favours post-treatment

b)



c)

First author, year, reference	Post-treatment Mean	SD	Total	Pre-treatment Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Benralizumab								
Menzella 2021 [68]	17.8	4.6	32	15.3	3.9	32	4.1	2.50 (0.41–4.59)
Numata 2022 [77]	20.7	2.9	23	18.8	5.2	23	3.7	1.90 (−0.53–4.33)
Padilla-Galo 2021 [80]	21.3	2.2	44	13.7	4.1	44	5.0	7.60 (6.23–8.97)
Subtotal (95% CI)			**99**			**99**	**12.8**	**4.09 (0.13–8.05)**
Heterogeneity: Tau²=11.21, Chi²=25.15, df=2 (p<0.0001); I²=92%								
Test for overall effect: z=2.02 (p=0.04)								
Mepolizumab								
Bagnasco 2020 [16]	22.0	3.0	138	17.0	5.0	138	5.5	5.00 (4.03–5.97)
Carpagnano 2020 [24]	21.9	2.7	41	12.0	2.7	41	5.3	9.90 (8.73–11.07)
Crimi 2021 [29]	21.8	3.1	32	13.8	4.7	32	4.3	8.00 (6.05–9.95)
Detoraki 2021 [32]	22.3	4.5	44	12.1	4.4	44	4.4	10.20 (8.34–12.06)
Domingo 2021 [35]	20.8	3.1	318	14.1	5.0	318	5.8	6.70 (6.05–7.35)
Enríquez-Rodríguez 2021 [39]	17.5	4.8	69	13.2	4.4	69	4.8	4.30 (2.76–5.84)
González-Pérez 2022 [43]	18.9	4.8	61	13.8	4.6	61	4.6	5.10 (3.43–6.77)
Kallieri 2022 [51]	21.9	3.6	169	15.2	4.5	169	5.6	6.70 (5.83–7.57)
Koistinen 2022 [56]	18.96	4.59	51	14.2	5.45	51	4.3	4.76 (2.80–6.72)
Koya 2020 [57]	22.0	3.6	3	14.7	6.1	3	0.8	7.30 (−0.72–15.32)
Matucci 2022 [64]	22.2	3.2	51	15.3	4.3	51	4.9	6.90 (5.43–8.37)
Menzella 2021 [68]	22.7	2.5	83	15.3	4.2	83	5.4	7.40 (6.35–8.45)
Özdel Öztürk 2021 [79]	22.03	4.31	62	16.6	5.51	62	4.6	5.43 (3.69–7.17)
Pelaia 2020 [81]	21.08	3.35	88	12.55	3.72	88	5.4	8.53 (7.48–9.58)
Schleich 2020 [91]	15.1	4.2	116	11.2	5.3	116	5.2	3.90 (2.67–5.13)
Sposato 2020 [95]	20.5	2.8	134	14.2	4.4	134	5.6	6.30 (5.42–7.18)
Subtotal (95% CI)			**1460**			**1460**	**76.3**	**6.62 (5.77–7.46)**
Heterogeneity: Tau²=2.32, Chi²=108.69, df=9 (p<0.00001); I²=86%								
Test for overall effect: z=15.38 (p<0.00001)								
Benralizumab/mepolizumab								
Menigoz 2022 [67]	20.4	2.3	110	12.8	5.4	110	5.3	7.60 (6.50–8.70)
Subtotal (95% CI)			**110**			**110**	**5.3**	**7.60 (6.50–8.70)**
Heterogeneity: not applicable								
Test for overall effect: z=15.27 (p<0.00001)								
Reslizumab								
Pérez de Llano 2022 [83]	20	5.1	208	12.8	4.5	208	5.5	7.20 (6.28–8.12)
Subtotal (95% CI)			**208**			**208**	**5.5**	**7.20 (6.28–8.12)**
Heterogeneity: not applicable								
Test for overall effect: z=15.27 (p<0.00001)								
Total (95% CI)			**1877**			**1877**	**100**	**6.41 (5.66–7.16)**
Heterogeneity: Tau²=2.40, Chi²=144.55, df=20 (p<0.00001); I²=86%								
Test for overall effect: z=16.82 (p<0.00001)								
Test for subgroup differences: Chi²=4.19, df=3 (p=0.24); I²=28.5%								

Mean difference IV, random, 95% CI

−10 −5 0 5 10

Favours post-treatment

d)

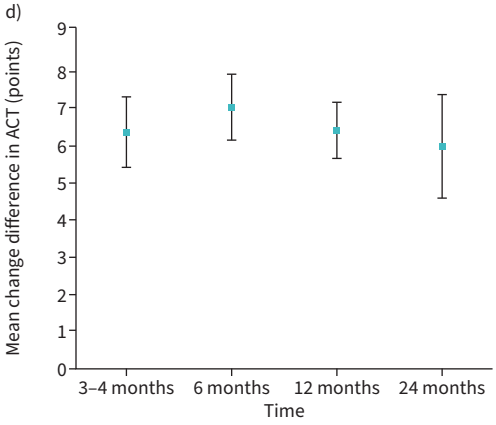


FIGURE 4 a) Forest plot of the mean change in asthma control questionnaire (ACQ) score after 12 months of anti-interleukin (IL)5/5Rα treatment compared to pre-treatment. Sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. b) Variation over time of the mean change in ACQ score after anti-IL-5/5Rα treatment compared to pre-treatment. Interval plots display 95% confidence intervals for the mean difference. c) Forest plot of the mean change in asthma control test (ACT) score after 12 months of anti-IL-5/5Rα treatment compared to pre-treatment. Sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. d) Variation over time of the mean change in ACT score after anti-IL-5/5Rα treatment compared to pre-treatment. Interval plots display 95% confidence intervals for the mean difference. IV: inverse variance.

outcomes pre-treatment and at 3–4, 6, 12 and 24 months of treatment, depending on the available data. We performed subgroup analysis according to the specific anti-IL-5 administered in each study. Sensitivity analysis was performed using the fixed-effect model and excluding studies with fewer than 20 participants.

Results

Study identification and selection

The search identified 6401 studies, of which 92 published studies with 9546 participants were shortlisted for inclusion in the systematic review and meta-analysis. 88 studies were observational (23 prospective and 65 retrospective), while four were nonrandomised clinical trials. Participants received mepolizumab in 52 studies (n=5628–59%), benralizumab in 25 studies (2309–24.2%), reslizumab in four studies (583–6.2%), either mepolizumab or benralizumab in nine studies (929–9.8%), either mepolizumab or reslizumab in one study (16–0.01%) and either mepolizumab or benralizumab or reslizumab in one study (81–0.8%). Figure 1 shows the flowchart of the study selection process (in detail in supplementary appendix 3) and table 1 shows the characteristics of the included studies.

Study outcomes

Primary outcome effect of biologics on exacerbations

Anti-IL-5/5Rα reduced the annual rate of severe exacerbations by 3.07 events·patient^{-1}·year^{-1} (95% CI −3.60–−2.54; I^2=98%) in 31 studies with 3742 patients and the risk of severe exacerbations decreased by 62% (risk ratio 0.38, 95% CI 0.29–0.50; I^2=97%) in 11 studies with 2501 patients at 12 months of treatment, compared to pre-treatment (figures 2a and 2b, respectively). At 24 months of treatment, the annual rate of severe exacerbations was reduced by 3.77 events·patient^{-1}·year^{-1} (95% CI −4.73–−2.80; I^2=90%) and risk reduced by 73% (risk ratio 0.27, 95% CI 0.23–0.33) (figures 2c and 2d, respectively).

Effect of biologics on hospitalisations due to asthma exacerbation

Anti-IL-5/5Rα reduced the annual rate of hospitalisations by 0.26 events·patient^{-1}·year^{-1} (95% CI −0.34–−0.18; I^2=91%) (figure 3a) and the risk of hospitalisations by 54% (risk ratio 0.46, 95% CI 0.35–0.61; I^2=51%) at 12 months (figure 3b). At 24 months, the annual rate of hospitalisations decreased by 0.43 (95% CI −0.63–−0.23; I^2=0%) (figure 3c).

Effect of biologics on asthma control, symptoms and quality of life

Change in ACQ score

17 studies with 2890 patients reported a change in ACQ score with an MD of −1.11 points (95% CI −1.29–−0.94; I^2=85%) at 12 months of treatment (figure 4a). This improvement was present at 3–4 months (MD −1.35, 95% CI −1.86–−0.85; I^2=20%) (supplementary figure E1), 6 months (MD −1.28, 95% CI −1.60–−0.96; I^2=73%) (supplementary figure E2) and even greater at 24 months (MD −2.26, 95% CI −2.51–−2.00; I^2=0%) (supplementary figure E3). The MD reached the minimal clinically important difference (MCID) for the ACQ (−0.50 points) at all time-points [107]. The improvement in ACQ score over time is presented in figure 4b.

Change in ACT score

Anti-IL-5/5Rα increased the ACT score by 6.41 points (95% CI 5.66–7.16; I^2=86%) at 12 months (figure 4c). This improvement was also observed at 3–4 months (MD 6.38, 95% CI 5.43–7.33; I^2=71%) (supplementary figure E4), 6 months (MD 7.03, 95% CI 6.15–7.91; I^2=88%) (supplementary figure E5) and 24 months (MD 5.99, 95% CI 4.60–7.37; I^2=72%) (supplementary figure E6). The MD reached the MCID for the ACT (three points) at all time-points [108]. The improvement in ACT score over time is presented in figure 4d.

a)

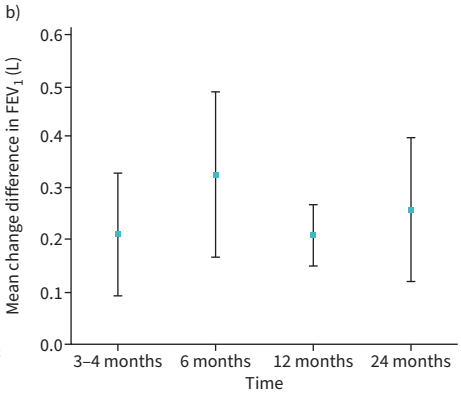
First author, year, reference	Post-treatment Mean	SD	Total	Pre-treatment Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Benralizumab								
D'Ancona 2021 [31]	1.84	0.52	89	1.72	0.66	89	5.9	0.12 (−0.05–0.29)
Jackson 2022 [49]	2.0	0.8	208	1.85	0.8	208	6.6	0.15 (−0.00–0.30)
Kavanagh 2021 [53]	1.9	0.7	130	1.76	0.69	130	6.1	0.14 (−0.03–0.31)
Menzella 2021 [68]	2.4	1.0	32	1.8	0.8	32	1.6	0.60 (0.16–1.04)
Padilla-Galo 2021 [80]	1.83	0.556	44	1.46	0.509	44	4.5	0.37 (0.15–0.59)
Subtotal (95% CI)			**503**			**503**	**24.6**	**0.21 (0.09–0.33)**
Heterogeneity: Tau²=0.01, Chi²=7.00, df=4 (p=0.14); I²=43%								
Test for overall effect: z=3.42 (p=0.0006)								
Mepolizumab								
Bagnasco 2020 [16]	2.36	0.88	138	2.03	0.78	138	52.2	0.33 (0.13–0.53)
Brás 2021 [20]	2.2	0.8	20	2.1	0.9	20	1.2	0.10 (−0.43–0.63)
Carpagnano 2020 [24]	1.86	0.52	41	1.56	0.45	41	4.8	0.30 (0.09–0.51)
D'Ancona 2020 [30]	1.85	0.81	91	1.91	0.83	91	4.1	−0.06 (−0.30–0.18)
Drick 2018 [36]	2.4	0.95	32	1.8	0.5	32	2.1	0.60 (0.23–0.97)
Enríquez-Rodríguez 2021 [39]	2.06	0.569	69	1.883	0.553	69	5.5	0.18 (−0.01–0.36)
González-Pérez 2022 [43]	2.6	0.7	61	2.28	0.72	61	3.8	0.32 (0.07–0.57)
Kallieri 2022 [51]	2.09	0.7	169	1.87	0.7	169	6.8	0.22 (0.07–0.37)
Kavanagh 2020 [52]	1.82	0.72	99	1.85	0.72	99	5.1	−0.03 (−0.23–0.17)
Matucci 2022 [64]	2.51	0.8	51	2.16	0.8	51	2.8	0.35 (0.04–0.66)
Menzella 2021 [68]	2.2	0.8	83	1.9	0.8	83	4.0	0.30 (0.06–0.54)
Özdel Öztürk 2021 [79]	2.7	1.11	62	2.1	0.94	62	2.2	0.60 (0.24–0.96)
Schleich 2020 [91]	2.12	1.2	116	2.03	0.81	116	3.6	0.09 (−0.17–0.35)
Sposato 2020 [95]	2.21	0.8	134	2.0	0.8	134	5.3	0.21 (0.02–0.40)
Yilmaz 2021 [106]	1.977	0.8	41	2.117	0.872	41	2.2	−0.14 (−0.50–0.22)
Subtotal (95% CI)			**1207**			**1207**	**58.6**	**−0.12 (0.13–0.30)**
Heterogeneity: Tau²=0.01, Chi²=27.98, df=14 (p=0.01); I²=50%								
Test for overall effect: z=4.71 (p<0.00001)								
Benralizumab/mepolizumab								
Dhariwal 2021 [33]	1.93	0.64	153	1.79	0.68	153	6.9	0.14 (−0.01–0.29)
Voelker 2020 [103]	2.1	0.9	110	2.0	0.9	110	2.8	0.10 (−0.21–0.41)
Subtotal (95% CI)			**216**			**216**	**9.6**	**0.13 (0.00–0.27)**
Heterogeneity: Tau²=0.00, Chi²=0.05, df=1 (p=0.82); I²=0%								
Test for overall effect: z=1.94 (p=0.05)								
Reslizumab								
Pérez de Llano 2022 [83]	2.09	0.75	208	1.85	0.73	208	7.1	0.24 (0.10–0.38)
Subtotal (95% CI)			**208**			**208**	**7.1**	**0.24 (0.10–0.38)**
Heterogeneity: not applicable								
Test for overall effect: z=3.31 (p=0.0009)								
Total (95% CI)			**2134**			**2134**	**100**	**0.21 (0.15–0.27)**
Heterogeneity: Tau²=0.01, Chi²=36.43, df=22 (p=0.03); I²=40%								
Test for overall effect: z=6.76 (p<0.00001)								
Test for subgroup differences: Chi²=1.39, df=3 (p=0.71); I²=0%								

Mean difference IV, random, 95% CI

−1.0 −0.5 0.0 0.5 1.0

Favours post-treatment

b)



c)

First author, year, reference	Post-treatment Mean	SD	Total	Pre-treatment Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Benralizumab								
D'Ancona 2021 [31]	71.5	18.4	89	64.5	21.6	89	4.5	7.00 (1.11–12.89)
Menzella 2021 [68]	80.9	23.5	32	60.0	19.8	32	2.8	20.90 (10.25–31.55)
Padilla-Galo 2021 [80]	78.3	15.0	44	66.1	14.0	44	4.5	12.20 (6.14–18.26)
Sposato 2022 [96]	87.9	20.8	95	74.1	24.9	95	4.3	13.80 (7.28–20.32)
Subtotal (95% CI)			**260**			**260**	**16.1**	**12.37 (7.57–17.17)**
Heterogeneity: Tau²=11.21, Chi²=5.73, df=3 (p=0.13); I²=48%								
Test for overall effect: z=5.05 (p<0.00001)								
Mepolizumab								
Atayik 2022 [15]	84.1	12.52	57	62.18	15.7	57	4.8	21.92 (16.71–27.13)
Carpagnano 2020 [24]	75.2	12.7	41	64.0	13.2	41	4.7	11.20 (5.59–16.81)
Crimi 2021 [29]	83.1	20.2	32	76.6	20.9	32	3.0	6.50 (−3.57–16.57)
D'Ancona 2020 [30]	63.6	21.6	91	65.8	22.2	91	4.3	−2.20 (−8.56–4.16)
Detoraki 2021 [32]	81.0	23.0	44	69.0	23.0	44	3.1	12.00 (2.39–21.61)
Drick 2018 [36]	73.0	33.0	32	55.0	10.5	32	2.5	18.00 (6.00–30.00)
Eldaboussi 2021 [38]	75.4	10.7	53	59.6	12.3	53	5.1	15.80 (11.41–20.19)
Enríquez-Rodríguez 2021 [39]	76.0	21.0	69	68.0	20.0	69	4.1	8.00 (1.16–14.84)
González-Pérez 2022 [43]	80.95	18.17	61	72.75	17.85	61	4.3	8.20 (1.81–14.59)
Harvey 2020 [44]	62.4	23.0	309	56.9	17.78	309	5.6	5.50 (2.26–8.74)
Kallieri 2020 [50]	74.3	18.0	70	67.0	17.0	70	4.6	7.30 (1.50–13.10)
Koya 2020 [57]	78.6	38.6	3	76.1	40.9	3	0.1	2.50 (−61.14–66.14)
Kurosawa 2019 [59]	72.3	9.1	32	69.4	11.8	32	4.8	2.90 (−2.26–8.06)
Maglio 2021 [61]	73.9	16.9	105	63.7	17.9	105	5.0	10.20 (5.49–14.91)
McDowell 2022 [66]	70.1	21.7	101	68.9	19.0	101	4.6	1.20 (−4.42–6.82)
Menzella 2021 [68]	82.3	15.9	83	70.9	19.7	83	4.7	11.40 (5.95–16.85)
Özdel Öztürk 2021 [79]	91.18	32.98	62	70.89	24.25	62	3.0	20.29 (10.10–30.48)
Sposato 2020 [95]	78.0	20.0	134	72.0	21.0	134	4.9	6.00 (1.09–10.91)
Yilmaz 2021 [106]	78.9	23.5	41	78.9	23.2	41	3.0	0.00 (−10.11–10.11)
Subtotal (95% CI)			**1420**			**1420**	**76.4**	**8.89 (5.93–11.85)**
Heterogeneity: Tau²=29.59, Chi²=75.79, df=18 (p<0.00001); I²=76%								
Test for overall effect: z=5.88 (p<0.00001)								
Benralizumab/mepolizumab								
Menigoz 2022 [67]	71	24	110	63	23	110	4.4	8.00 (1.79–14.21)
Subtotal (95% CI)			**110**			**110**	**4.4**	**8.00 (1.79–14.21)**
Heterogeneity: not applicable								
Test for overall effect: z=2.52 (p=0.01)								
Reslizumab								
Ibrahim 2019 [46]	70.61	15.4	26	62.08	19.85	26	3.1	8.53 (−1.13–18.19)
Subtotal (95% CI)			**26**			**26**	**3.1**	**8.53 (−1.13–18.19)**
Heterogeneity: not applicable								
Test for overall effect: z=1.73 (p=0.08)								
Total (95% CI)			**1816**			**1877**	**100**	**9.44 (7.01–11.86)**
Heterogeneity: Tau²=24.72, Chi²=84.50, df=24 (p<0.00001); I²=72%								
Test for overall effect: z=7.63 (p<0.00001)								
Test for subgroup differences: Chi²=1.80, df=3 (p=0.61); I²=0%								

Mean difference IV, random, 95% CI

−20 −10 0 10 20

Favours post-treatment

d)

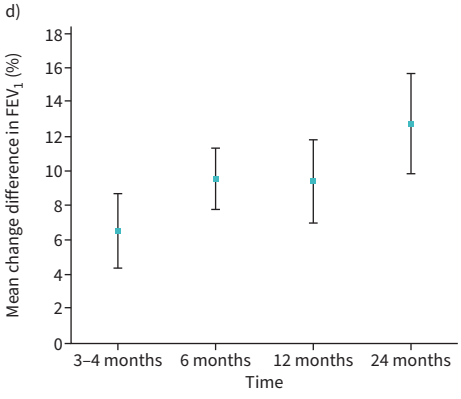


FIGURE 5 a) Forest plot of the mean change in forced expiratory volume in 1 s (FEV_1) in litres after 12 months of anti-interleukin (IL)5/5Rα treatment compared to pre-treatment. Sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. b) Variation over time of the mean change in FEV_1 in litres after anti-IL-5/5Rα treatment compared to pre-treatment. Interval plots display 95% confidence intervals for the mean difference. c) Forest plot of the mean change in FEV_1 % predicted after 12 months of anti-IL-5/5Rα treatment compared to pre-treatment. Sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. d) Variation over time of the mean change in FEV_1 % predicted after anti-IL-5/5Rα treatment compared to pre-treatment. Interval plots display 95% confidence intervals for the mean difference. IV: inverse variance.

Change in AQLQ score

Anti-IL-5/5Rα increased the AQLQ score by 1.08 points (95% CI 0.88–1.28; I^2=71%) at 12 months (supplementary figure E7). This improvement was observed at 3–4 months (MD 1.16, 95% CI 0.98–1.33; I^2=0%) (supplementary figure E8) and 6 months (MD 1.17, 95% CI 0.99–1.35; I^2=0%) (supplementary figure E9); no studies reported AQLQ results at 24 months. The MD reached the MCID for the AQLQ (0.50 points) at all time points [109]. The improvement in AQLQ score over time is presented in supplementary figure E10.

Effect of biologics on lung function

Anti-IL-5/5Rα improved FEV_1 by 0.21 L (95% CI 0.15–0.27; I^2=40%) at 12 months (figure 5a). This improvement was present at 3–4 months (MD 0.21 L, 95% CI 0.09–0.34; I^2=49%) (supplementary figure E11), 6 months (MD 0.33 L, 95% CI 0.17–0.50; I^2=79%) (supplementary figure E12) and 24 months (MD 0.26 L, 95% CI 0.12–0.41; I^2=33%) (supplementary figure E13). Moreover, FEV_1 improved by 9.44% pred (95% CI 7.01–11.86; I^2=72%) at 12 months (figure 5c). This improvement was also present at 3–4 months (MD 6.40%, 95% CI 4.22–8.57; I^2=0%) (supplementary figure E14), 6 months (MD 9.52, 95% CI 7.79–11.24; I^2=3%) (supplementary figure E15) and 24 months (MD 12.74, 95% CI 9.79–15.70; I^2=0%) (supplementary figure E16). The improvement in FEV_1 (L and % predicted) over time is depicted in figures 5b and 5d, respectively.

Effect of biologics on OCS use

Number of patients receiving OCS

There was a reduction in OCS use by 51% at 12 months (risk ratio 0.49, 95% CI 0.42–0.56; I^2=93) (figure 6a). This improvement was present at 3–4 months (risk ratio 0.61, 95% CI 0.49–0.77; I^2=77%) (supplementary figure E17), 6 months (risk ratio 0.58, 95% CI 0.50–0.68; I^2=79%) (supplementary figure E18) and was greater at 24 months (risk ratio 0.35, 95% CI 0.27–0.45; I^2=57%) (supplementary figure E19). The reduction in the number of patients receiving OCS over time is depicted in figure 6b.

OCS dose (mg prednisolone·day^{-1})

The mean OCS dose decreased by 6.01 mg·day^{-1} (95% CI −7.55–−4.48; I^2=92%) at 12 months (figure 6c). Reduction of the daily OCS use was evident at 3–4 months (MD −6.69 mg·day^{-1}, 95% CI −8.68–−4.71; I^2=48%) (supplementary figure E20) and persisted at 6 months (MD −7.03 mg·day^{-1}, 95% CI −9.91–−4.16; I^2=94%) (supplementary figure E21) and 24 months (MD −8.45 mg·day^{-1}, 95% CI −12.23–−4.68; I^2=95%) (supplementary figure E22). The reduction in OCS dose over time is depicted in figure 6d.

OCS reduction to doses <5 mg prednisolone·day^{-1}

Patients on anti-IL-5/5Rα were approximately four times more likely to use such low doses after 12 months (risk ratio 4.01, 95% CI 1.20–13.39; I^2=98%) (supplementary figure E23).

Effect of biologics on asthma biomarkers

Blood eosinophil count

The use of anti-IL-5/5Rα reduced blood eosinophils by 568.5 cells·μL^{-1} (95% CI −679.5–−457.6; I^2=96%) at 12 months (figure 7a). This improvement was observed from the first 3–4 months of treatment (MD −614.8 cells·μL^{-1} , 95% CI −662–−567.5; I^2=23%) (supplementary figure E24), 6 months (MD −641.3 cells·μL^{-1} , 95% CI −776.2–−506.4; I^2=79%) (supplementary figure E25) and 24 months (MD −674.9 cells·μL^{-1} , 95% CI −822.5–−527.3; I^2=75%) (supplementary figure E26). The reduction in the number of blood eosinophils over time is depicted in figure 7b.

a)

First author, year, reference	Post-treatment Events	Total	Pre-treatment Events	Total	Weight (%)	Risk ratio M-H, random, 95% CI
Benralizumab						
Chung 2022 [27]	165	204	202	204	3.0	0.82 (0.76–0.87)
d'Ancona 2021 [31]	41	89	89	89	2.8	0.46 (0.37–0.58)
Jackson 2022 [49]	60	208	127	208	2.8	0.47 (0.37–0.60)
Kavanagh 2021 [53]	36	130	74	130	2.7	0.49 (0.35–0.67)
Kayser 2021 [54]	18	64	36	64	2.4	0.50 (0.32–0.78)
Menzies-Gow 2022 [70]	222	598	598	598	3.0	0.37 (0.33–0.41)
Miralles López 2022 [71]	15	84	39	84	2.2	0.38 (0.23–0.64)
Padilla-Galo 2021 [80]	8	44	18	44	1.1	0.44 (0.22–0.91)
Subtotal (95% CI)		**1421**		**1421**	**20.6**	**0.48 (0.32–0.72)**
Total events	**565**		**1183**			
Heterogeneity: Tau²=0.31, Chi²=260.99, df=7 (p<0.00001); I²=97%						
Test for overall effect: z=3.51 (p=0.0004)						
Mepolizumab						
Brás 2021 [20]	2	20	6	20	0.7	0.33 (0.08–1.46)
Carpagnano 2020 [24]	2	41	19	41	0.8	0.11 (0.03–0.42)
d'Ancona 2020 [30]	44	91	91	91	2.8	0.49 (0.39–0.60)
Domingo 2021 [35]	55	318	98	318	2.7	0.56 (0.42–0.75)
Drick 2018 [36]	8	32	17	32	1.8	0.47 (0.24–0.93)
Eldaboussi 2021 [38]	5	53	45	53	1.5	0.11 (0.05–0.26)
Enríquez-Rodríguez 2021 [39]	13	69	25	69	2.1	0.52 (0.29–0.93)
Fong 2021 [41]	32	62	41	62	2.7	0.78 (0.58–1.05)
González-Pérez 2022 [43]	2	61	10	61	0.7	0.20 (0.05–0.88)
Kallieri 2020 [50]	27	70	42	70	2.6	0.64 (0.45–0.91)
Kavanagh 2020 [52]	29	99	68	99	2.6	0.43 (0.31–0.60)
Kayser 2021 [54]	34	123	74	123	2.6	0.46 (0.33–0.63)
Koistinen 2022 [56]	42	51	46	51	2.9	0.91 (0.78–1.07)
Koya 2020 [57]	1	3	2	3	0.6	0.50 (0.08–2.99)
Kurosawa 2019 [59]	0	32	9	32	0.3	0.05 (0.00–0.87)
Llanos 2020 [60]	276	346	320	346	3.0	0.86 (0.81–0.92)
Maglio 2021 [61]	10	105	54	105	2.0	0.19 (0.10–0.34)
Matucci 2022 [64]	32	51	41	51	2.8	0.78 (0.61–1.00)
McDowell 2022 [66]	53	101	83	101	2.9	0.64 (0.52–0.79)
Nagase 2021 [73]	10	61	16	61	1.8	0.63 (0.31–1.27)
Numata 2019 [76]	16	27	16	27	2.4	1.00 (0.64–1.56)
Özdel Öztürk 2021 [79]	20	62	50	62	2.5	0.40 (0.27–0.59)
Pelaia 2020 [81]	11	88	67	88	2.1	0.16 (0.09–0.29)
Pilette 2022 [85]	222	822	319	822	2.9	0.70 (0.60–0.80)
Pini 2021 [86]	38	87	39	87	2.6	0.97 (0.70–1.36)
Silver 2020 [94]	21	527	106	527	2.3	0.20 (0.13–0.31)
Strauss 2018 [97]	6	36	13	36	1.5	0.46 (0.20–1.08)
Taillé 2020 [98]	60	146	135	146	2.9	0.44 (0.36–0.54)
Thomas 2021 [99]	96	300	143	300	2.9	0.67 (0.55–0.82)
van Toor 2021 [101]	12	78	40	78	2.1	0.30 (0.17–0.53)
Subtotal (95% CI)		**3962**		**3962**	**64.1**	**0.49 (0.41–0.59)**
Total events	**1179**		**2035**			
Heterogeneity: Tau²=0.19, Chi²=334.13, df=29 (p<0.00001); I²=91%						
Test for overall effect: z=7.62 (p<0.00001)						
Benralizumab/mepolizumab						
Dhariwal 2021 [33]	32	153	97	153	2.6	0.33 (0.24–0.46)
Menigoz 2022 [67]	29	110	70	110	2.6	0.41 (0.29–0.58)
Subtotal (95% CI)		**263**		**263**	**5.2**	**0.37 (0.29–0.47)**
Total events	**61**		**167**			
Heterogeneity: Tau²=0.00, Chi²=0.88, df=1 (p=0.35); I²=0%						
Test for overall effect: z=8.23 (p<0.00001)						
Reslizumab						
Hashimoto 2022 [45]	52	134	77	134	2.8	0.68 (0.52–0.87)
Ibrahim 2019 [46]	9	26	14	26	1.9	0.64 (0.34–1.22)
Pérez de Llano 2022 [83]	38	208	114	208	2.7	0.33 (0.24–0.46)
Subtotal (95% CI)		**368**		**368**	**7.4**	**0.52 (0.30–0.88)**
Total events	**99**		**205**			
Heterogeneity: Tau²=0.18, Chi²=12.67, df=2 (p=0.002); I²=84%						
Test for overall effect: z=2.43 (p=0.01)						
Benralizumab/mepolizumab/reslizumab						
Bjerrum 2021 [19]	39	81	61	81	2.0	0.64 (0.49–0.83)
Subtotal (95% CI)		**81**		**81**	**2.8**	**0.64 (0.49–0.83)**
Total events	**39**		**167**			
Heterogeneity: not applicable						
Test for overall effect: z=3.49 (p=0.0007)						
Total (95% CI)		**6095**		**6095**	**100**	**0.49 (0.42–0.56)**
Total events	**1943**		**3651**			
Heterogeneity: Tau²=0.19, Chi²=653.49, df=43 (p<0.00001); I²=93%						
Test for overall effect: z=9.60 (p<0.00001)						
Test for subgroup differences: Chi²=9.61, df=4 (p=0.05); I²=58.4%						

Risk ratio M-H, random, 95% CI

0.1 0.2 0.5 1.0 2.0 5.0 10.0

Favours post-treatment

c)

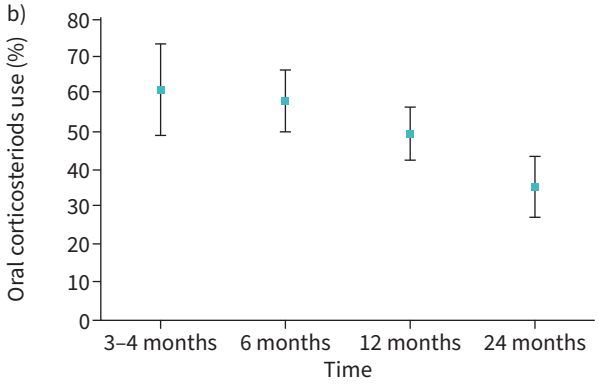
First author, year, reference	Post-treatment Mean	sd	Total	Pre-treatment Mean	sd	Total	Weight (%)	Mean difference IV, random, 95% CI
Benralizumab								
Chung 2022 [27]	24.93	17.73	204	30.63	11.72	204	4.5	−5.70 (−8.62–−2.78)
d'Ancona 2021 [31]	3.3	1.6	89	12.4	9.4	89	5.0	−9.10 (−11.08–−7.12)
Jackson 2022 [49]	5.4	10.8	208	13.9	12.1	208	4.9	−8.50 (−10.70–−6.30)
Menzella 2021 [68]	3.4	7.5	32	4.4	7.7	32	4.1	−1.00 (−4.72–2.72)
Padilla-Galo 2021 [80]	3.9	7.2	44	19.3	8.8	44	4.3	−15.40 (−18.76–−12.04)
Subtotal (95% CI)			**577**			**577**	**22.8**	**−8.01 (−11.61–−4.40)**
Heterogeneity: Tau²=14.77, Chi²=35.62, df=4 (p<0.00001); I²=89%								
Test for overall effect: z=4.35 (p<0.0001)								
Mepolizumab								
Bagnasco 2020 [16]	2.0	4.2	138	10.1	9.4	138	5.1	−8.10 (−9.82–−6.38)
d'Ancona 2020 [30]	1.6	1.2	91	10.0	5.4	91	5.3	−8.40 (−9.54–−7.26)
Detoraki 2021 [32]	1.1	3.7	44	8.6	11.2	44	4.2	−7.50 (−10.99–−4.01)
Drick 2018 [36]	4.5	0.85	32	5.0	2.5	32	5.3	−0.50 (−1.41–0.41)
Eldaboussi 2021 [38]	0.75	1.3	53	5.8	6.2	53	5.1	−5.05 (−6.76–−3.34)
Enríquez-Rodríguez 2021 [39]	9.0	10.9	69	18.0	14.2	69	3.8	−9.00 (−13.22–−4.78)
González-Pérez 2022 [43]	6.5	4.2	61	11.3	9.6	61	4.7	−4.80 (−7.43–−2.17)
Kallieri 2020 [50]	4.5	6.1	70	10.1	7.0	70	4.9	−5.60 (−7.78–−3.42)
Koistinen 2022 [56]	5.97	4.5	51	9.8	5.66	51	5.0	−3.83 (−5.81–−1.85)
Koya 2020 [57]	1.3	2.3	3	5.8	5.2	3	2.8	−4.50(−10.93–1.93)
Matucci 2022 [64]	2.4	2.0	51	7.3	4.3	51	5.2	−4.90 (−6.20–−3.60)
Menzella 2021 [68]	1.1	4.6	83	11.0	27.8	83	2.9	−9.90 (−15.96–−3.84)
Numata 2019 [76]	5.0	5.8	27	8.4	5.6	27	4.5	−3.40 (−6.44–−0.36)
Silver 2020 [94]	4.5	6.9	527	6.7	7.8	527	5.3	−2.20 (−3.09–−1.31)
Taillé 2020 [98]	8.3	15.9	146	20.6	16.5	146	4.1	−12.30 (−16.02–−8.58)
Subtotal (95% CI)			**1446**			**1446**	**68.2**	**−5.74 (−7.48–−4.00)**
Heterogeneity: Tau²=9.70, Chi²=188.81, df=14 (p<0.00001); I²=93%								
Test for overall effect: z=6.47 (p<0.00001)								
Benralizumab/mepolizumab								
Menigoz 2022 [67]	15	14.1	110	15.8	12.1	110	4.2	−0.80 (1.79–2.67)
Subtotal (95% CI)			**110**			**110**	4.2	**−0.80 (1.79–2.67)**
Heterogeneity: not applicable								
Test for overall effect: z=0.45 (p=0.65)								
Reslizumab								
Ibrahim 2019 [46]	4.77	4.53	26	9.29	4.32	26	4.8	−4.52 (−6.93–−2.11)
Subtotal (95% CI)			**26**			**26**	4.8	**−4.52 (−6.93–−2.11)**
Heterogeneity: not applicable								
Test for overall effect: z=3.68 (p=0.0002)								
Total (95% CI)			**2159**			**2159**	**100**	**−6.01 (−7.55–−4.48)**
Heterogeneity: Tau²=11.35, Chi²=273.05, df=21 (p<0.00001); I²=92%								
Test for overall effect: z=7.67 (p<0.00001)								
Test for subgroup differences: Chi²=9.14, df=3 (p=0.03); I²=67.2%								

Mean difference IV, random, 95% CI

−10 −5 0 5 10

Favours post-treatment

b)



d)

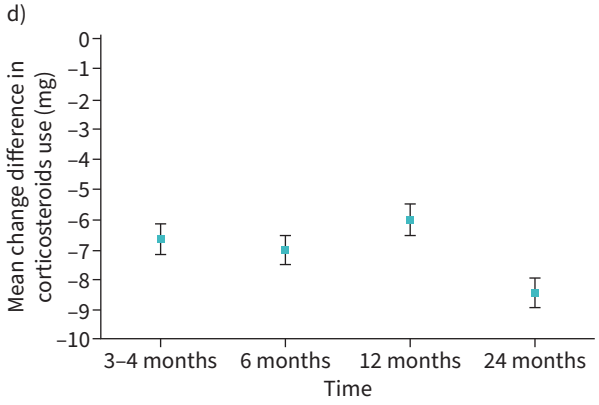


FIGURE 6 a) Forest plot of oral corticosteroids use relative risk after 12 months of anti-interleukin (IL)5/5Rα treatment compared to pre-treatment. Sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. b) Variation over time of the oral corticosteroids use relative risk after anti-IL-5/5Rα treatment compared to pre-treatment. Interval plots display 95% confidence intervals for the relative risk. c) Forest plot of the mean change in oral corticosteroids dose (mg) after 12 months of anti-IL-5/5Rα treatment compared to pre-treatment. Sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. d) Variation over time of the mean change in oral corticosteroids dose (mg) after anti-IL-5/5Rα treatment compared to pre-treatment. Interval plots display 95% confidence intervals for the mean difference. IV: inverse variance.

Sputum eosinophils

The use of anti-IL-5/5Rα was associated with a 31.9% reduction in sputum eosinophils (95% CI −60.4–−3.3; I^2=37%) at 12 months (supplementary figure E27).

F_{ENO}

The use of anti-IL-5/5Rα reduced F_{ENO} by 9.8 ppb (95% CI −17.2–−2.5; I^2=71%) at 12 months (figure 7c) and 24 months of treatment (MD −25.8, 95% CI −40.9–−10.6; I^2=50%) (supplementary figure E30). There was no significant decrease at 3–4 (supplementary figure E28) and 6 months of treatment (supplementary figure E29). The F_{ENO} change over time is presented in figure 7d.

IgE

Anti-IL-5/5Rα reduced IgE by 123.2 IU·mL^{-1} (95% CI −240.3–−6.1; I^2=30%) at 24 months (supplementary figure E34). There was no significant decrease at 3–4 (supplementary figure E32), 6 (supplementary figure E33) and 12 months (supplementary figure E31). The IgE change over time is presented in supplementary figure E35.

Risk of bias and sensitivity analysis

The risk of bias of eligible trials was assessed by the ROBINS-I tool (supplementary appendix 6) [11]. 53 studies (57%) were judged to be at moderate risk of bias, while 31 studies (34%) were at serious risk of bias, six (7%) at critical risk and two (2%) at low risk. Main sources of bias were confounding or missing data and the selection of reported results. Sensitivity analysis using the fixed-effect model (supplementary figures E36–E83) and excluding studies with fewer than 20 participants (supplementary figures E84–E131) yielded generally consistent results with our main analysis.

Discussion

This systematic review of 92 observational studies and nonrandomised clinical trials with 9546 patients receiving approved anti-IL-5/5Rα for severe eosinophilic asthma demonstrated a significant clinical and biomarker-related response to treatment. Specifically, anti-IL-5/5Rα reduced severe exacerbations and hospitalisations at 1 and 2 years and improved asthma control, quality of life and lung function at 3–4 months of treatment that persisted for up to 24 months of treatment. The response to biologics led to reductions in systemic corticosteroids use and asthma biomarkers (blood and sputum eosinophils, and to a lesser extent F_{ENO} and IgE). This is, to the best of our knowledge, the most comprehensive analysis of clinical and biomarker-related real-life effectiveness of anti-IL-5/5Rα biologics.

Exacerbations are central in the natural history of asthma, posing a significant healthcare use and socioeconomic burden [110]. In our study, patients responded to monoclonal antibodies showing marked reductions in the annual rates of severe exacerbations and hospitalisations at 12 and 24 months. These results are comparable with the results of the CALIMA and MENSA RCTs, where the annual rate of severe exacerbations was reduced by 2.5 and 3.0, respectively [5, 8], making the results of RCTs more generalisable. Biologics in real-life settings also reduced the risk of severe exacerbations by 62% and 73% at 12 and 24 months, as well as the risk of hospitalisations by 54% at 12 months. Our results further support the exacerbation-preventing role of anti-IL-5/5Rα in the long-term.

The use of biologics was associated with clinically relevant improvements in asthma control and quality of life, improving ACQ, ACT, and AQLQ at mean values higher than the MCIDs (0.5 points for ACQ and AQLQ, 3 points for ACT) [107–109]. Importantly, the improvement was evident as early as 3–4 months of use, with further enhancement until 24 months. Similar results were observed in the SOLANA study [111] where ACQ was reduced by 1.35 points, in the study by Bardelas *et al.* [112] where ACT was increased by 5.01 points by omalizumab, and in the study by Castro *et al.* [6] where AQLQ was increased by 1.08 points.

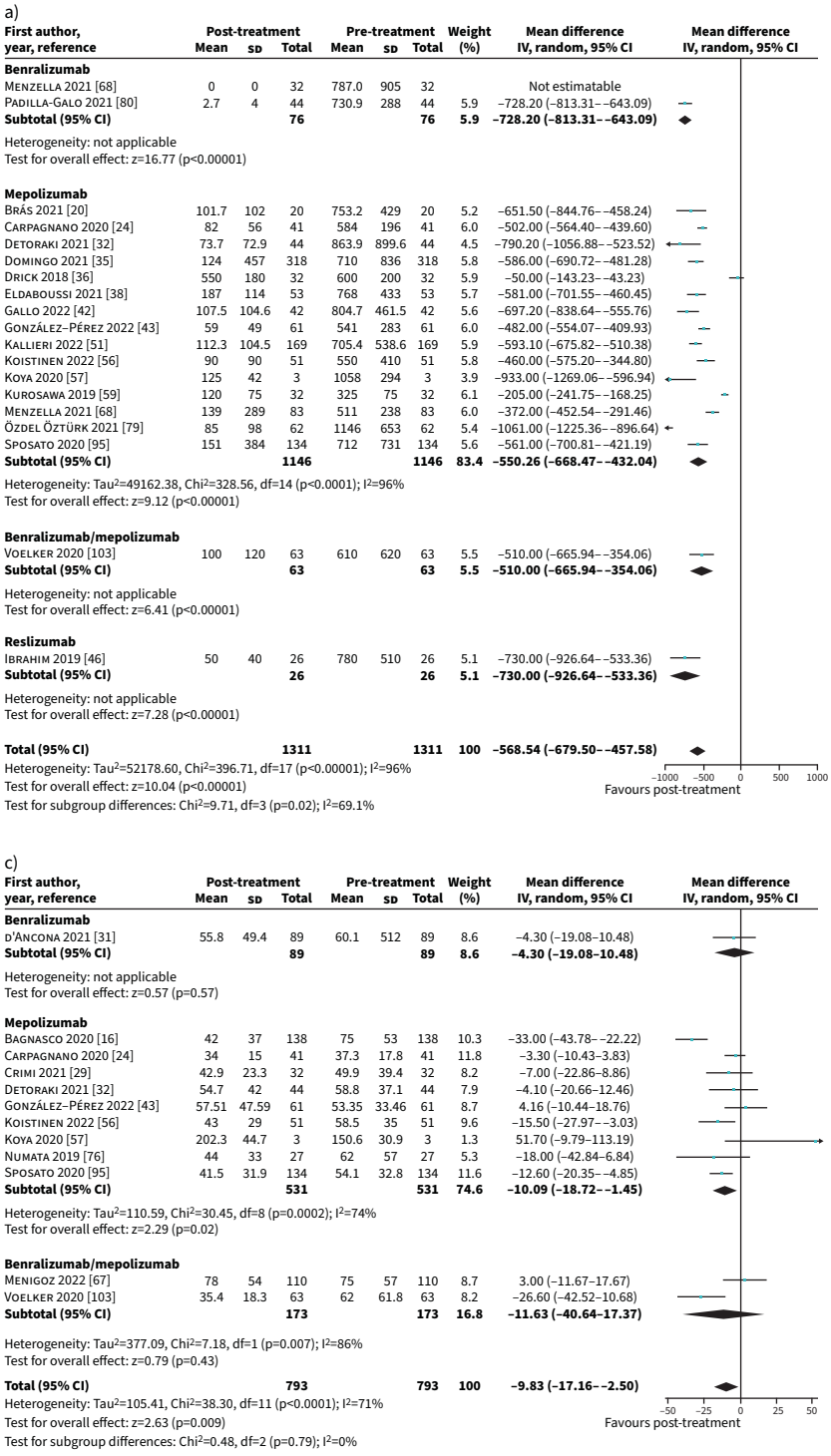


FIGURE 7 a) Forest plot of the mean change in the number of blood eosinophils·µL^{-1} after 12 months of anti-interleukin (IL)5/5Rα treatment compared to pre-treatment. Sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. b) Variation over time of the mean change in the number of blood eosinophils·µL^{-1} after anti-IL-5/5Rα treatment compared to pre-treatment. Interval plots display 95% confidence intervals for the mean difference. c) Forest plot of the mean change in fractional exhaled nitric oxide (F_{ENO}) ppb after 12 months of anti-IL-5/5Rα treatment compared to pre-treatment. Sample sizes are given for the total number of participants included in the study. Summary estimates presented separately for each biologic agent category. d) Variation over time of the mean change in F_{ENO} ppb after anti-IL-5/5Rα treatment compared to pre-treatment. Interval plots display 95% confidence intervals for the mean difference.

Lung function is important in patients with severe asthma, with healthcare efforts targeting to decelerate, preserve or optimally improve lung function parameters [113]. Anti-IL-5/5Rα biologics improved FEV_1 reaching the MCID of 0.2 L in asthma for all the time points from 3–4 to 24 months [114, 115]. The improvement was comparable to Bjermer *et al*. [7] (0.286 L); however inferior to SIROCCO (0.398 L and 0.248 L in patients with eosinophils ⩾300/μL and <300/μL, respectively) [9] suggesting that response may differ according to type-2 biomarkers.

Anti-IL-5/5Rα exhibited significant OCS sparing effect, reducing patients receiving OCS by 51% and the OCS dose by 6.01 $mg \cdot day^{-1}$. These results further support the efficacy of mepolizumab and benralizumab in the steroid sparing SIRIUS and ZONDA RCTs [116, 117]. In the PONENTE open-label single-arm study, 63% of steroid-dependent patients with severe eosinophilic asthma were able to discontinue OCS [70]. PONENTE used a rigorous approach to reduce OCS, yet our results further support the significant steroid-sparing effect of these biologics in real-life [70].

Our findings are consistent with RCTs assessing anti-IL-5/5Rα in terms of safety [6]. However, the external validity of RCTs is compromised, as many severe asthma patients are ineligible for RCTs due to their strict criteria. Therefore, our systematic review and meta-analysis of NRS supports the data from RCTs and the higher beneficial effect we observed in certain outcomes further expands the potential of these biologic agents in real-world patients [4, 5].

The main strength of our study is the holistic assessment of treatment response, exploring clinically relevant and biomarker-related outcomes at various time-points in a large number of studies and patients receiving all licensed anti-IL-5/5Rα biologics. Additionally, all real-life studies of these biologics have comparable pre-/post-designs, which justifies the rationale of our analysis. Our study also has certain limitations. First, we only included NRS, which limits our ability to assess causality between the intervention and outcomes, but we rigorously evaluated risk of bias, including confounding factors. Second, NRS are susceptible to missing data bias, especially at long-duration time-points such as 12 and 24 months, as only patients with an adequate response would continue on treatment, while patients reporting unfavourable outcomes may have discontinued therapy earlier and thus would be lost to follow-up at later time-points. Third, we did not pool data from some trials, due to lack of documentation of statistical measures or skewed data. However, we enhanced our meta-analyses using the generic inverse variance method to include studies that only reported risk ratios for events of interest. Fourth, we found significant heterogeneity in the measured outcomes. This was anticipated due to differences between the included NRS and between specific agents, which may be related to the availability of agents in different countries. Finally, we derived data regarding the classification of exacerbations from the individual studies included in the meta-analysis, with variations observed in the criteria used for the categorisation of exacerbations.

In conclusion, this systematic review, which included observational and nonrandomised clinical studies of all licensed anti-IL-5/5Rα monoclonal agents used in patients with severe eosinophilic asthma, demonstrated clinical effectiveness with reductions in exacerbations and hospitalisations, improvements in asthma control, quality of life and lung function, and decreased systemic corticosteroids use, as well as biomarker-related responses in real-life clinical practice.

Provenance: Submitted article, peer reviewed.

Data availability: Extracted data are available from the corresponding author on request.

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Author contributions: C. Kyriakopoulos and K. Kostikas developed the protocol. K. Kostikas and A. Gogali designed and C. Kyriakopoulos and E. Beris ran the literature search. C. Kyriakopoulos, E. Papadopoulou, K. Exarchos, D. Potonos, E. Beris, C. Aggelopoulou, S. Tryfon, A. Gogali and K. Kostikas screened records, extracted data and assessed risk of bias. C. Kyriakopoulos and D. Potonos independently extracted the estimates used in meta-analyses (the underlying data), and all authors had access to the extracted data and the scripts used for statistical analyses. E. Papadopoulou performed statistical analyses with input from C. Kyriakopoulos, S. Tryfon, A. Gogali and K. Kostikas. C. Kyriapoulos, E. Papadopoulou, A. Gogali, D. Potonos and K. Kostikas wrote the initial draft. All authors provided critical conceptual input, analysed and interpreted data, and critically revised subsequent drafts. All authors accept responsibility for the decision to submit for publication.

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