

Table S1. Baseline biomarkers, OCS use and biologics use in lower PBE cases (PBE <100 cells/ μ L)

Cases, n	8
PBE (/ μ L)	35.5 (22.0-41.0)
FeNO (ppb)	14.0 (7.8-18.5)
Sputum eosinophil (%)	0.0 (0.0-0.8)
Sputum neutrophil (%)	88.8 (84.2-90.0)
Sputum IL-6 (pg/mL)	976.7 (500.0-2108.6)
OCS use, n (%)	3 (37.5)
Biologics, n	anti-IL-4R 1, anti-IL-5/R 1, anti-IgE 3

FeNO, fraction of exhaled nitric oxide; OCS, oral corticosteroid; PBE, peripheral blood eosinophil count. Data are expressed as number (percentage) or median (interquartile)

Table S2. Correlations with sputum mediators after exclusion of patients with EGPA, ABPA(M) and COPD

	ECP	YKL-40	IL-6	IL-18	Tryptase
Age	0.08	0.09	0.08	0.17	0.10
BMI	0.02	0.09	0.04	-0.03	-0.08
Duration	0.08	-0.005	0.25	-0.04	0.1
PBE	0.54 [*]	-0.41 [*]	-0.46 [*]	-0.02	0.13
PBN	0.12	-0.08	-0.02	-0.03	-0.08
FeNO	0.41 [*]	-0.15	-0.26 [*]	0.25	0.20
IgE	0.35 [*]	-0.10	-0.21	0.06	0.13
%FEV ₁	-0.44 [*]	0.07	0.05	-0.02	0.05
Sputum eosinophil	0.84 [*]	-0.40 [*]	-0.26 [*]	-0.08	0.08
Sputum neutrophil	-0.53 [*]	0.50 [*]	0.30 [*]	0.26 [*]	0.03

ABPA(M), Allergic Bronchopulmonary Aspergillosis (Mycosis); BMI, body mass index; ECP, eosinophil cationic protein; EGPA, Eosinophilic Granulomatosis with polyangiitis; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; IgE, immunoglobulin E; PBE, peripheral blood eosinophil count; PBN, peripheral blood neutrophil count.

The data were expressed as r values which were calculated using Spearman's rank analysis. The asterisks indicate significant p value <0.05.

Table S3. Additional clinical characteristics supporting systemic–airway discordance across Parts A–C

	Part A (n=37)	Part B (n=9)	Part C (n=16)	P value
Allergic rhinitis, n (%)	19 (51.4%)	6 (66.7%)	6 (37.5%)	0.34
Eosinophilic Chronic Rhinosinusitis, n (%)	17 (45.9%)	5 (55.6%)	3 (18.8%)	0.10
Number of exacerbations in the previous year,	2 (0-5)	0 (0-2.5)	0.5 (0-3)	0.65
RAST positive for mite, n (%)	17 (45.9%)	4 (44.4%)	6 (37.5%)	0.94
RAST positive for aspergillus, n (%)	10 (27%)	0 (0%)	2 (12.5%)	0.16
RAST positive for pollen (ragweed or cedar), n (%)	16 (43.2%)	4 (44.4%)	4 (25%)	0.44
RAST positive for cockroach, n (%)	7 (18.9%)	2 (22.2%)	1 (6.25%)	0.55

RAST, Radioallergosorbent test. Data are expressed as number (percentage) or median (interquartile)

Table S4. Clinical characteristics across Parts A–C after exclusion of patients with EGPA, ABPA(M), and COPD (discordance defined as Part B)

	Part A (n=31)	Part B (n=9)	Part C (n=14)	p value
Age (years)	61 (50-66)	58 (49-67)	56.5 (43-63)	0.55
Women, n (%)	17 (54.8%)	6 (66.7%)	12 (85.7%)	0.13
BMI (kg/m ²)	23.3 (21.3-25.9)	22.7 (21.8-25.8)	23.4 (21.7-23.8)	0.95
Non-smoker, n (%)	19 (61.3%)	7 (77.8%)	13 (92.9%)	0.08
Disease duration (years)	14 (9-23)	30 (14-43)	10 (7-14.5)	0.09
ICS (µg/day; equivalent to fluticasone)	500 (500-800)	800 (750-1000)	500 (400-800)	0.14
mOCS, n (%)	5 (16.1%)	1 (11.1%)	3 (21.4%)	0.89
Severe disease, n (%)	27 (87.1%)	9 (100%)	10 (71.4%)	0.17
Exacerbation in previous year, n (%)	10 (32.3%)	4 (44.4%)	4 (28.6%)	0.79
PBE (/µL)	784 (529-1063.2) *#	137.5 (121.4-212.8)	121 (61.5-177.4)	<0.01
PBN (/µL)	3920 (3435-5075)	3690 (3370-3960)	4490 (3275-6952.5)	0.78
FeNO (ppb)	65 (40.5-102.5) *	55.5 (47-73.8) *	19.5 (13.5-27.5)	<0.01
IgE (IU/mL)	366 (143.5-1420) *	46.9 (25.5-137)	60.5 (28.2-100)	<0.01
%FEV ₁	83.8 (64.5-95.4) *	87.5 (83.4-97.9)	96.5 (89-104.6)	0.03
Sputum eosinophil (%)	39.2 (11-72.5) *	14 (8.4-29.5) *	0 (0-1.7)	<0.01
Sputum neutrophil (%)	33.7 (14.7-64.8) *	40 (10.6-64.2) *	85.4 (68.9-89.2)	<0.01
ECP (ng/mL)	1510.3 (442.6-1914.9) *	1478 (209.9-1685.4) *	185.1 (163.6-196.8)	<0.01
Tryptase (pg/mL)	15.7 (1.6-148.4)	12.5 (7.9-39.5)	8.4 (1.4-66.6)	0.90
YKL-40 (ng/mL)	59 (22.7-109.7)	85 (65.2-178.8)	133.6 (54.1-267.5)	0.08
IL-6 (pg/mL)	62.3 (30.2-163.7) #	518.5 (213.8-579.3)	176.5 (47.7-560.9)	0.01
IL-18 (pg/mL)	21.8 (8.8-113.4)	56.7 (22.7-78.5)	12.2 (4.4-229.1)	0.42

ABPA(M), Allergic Bronchopulmonary Aspergillosis (Mycosis); BMI, body mass index; ECP, eosinophil cationic protein; EGPA, Eosinophilic Granulomatosis with polyangiitis; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; IgE, immunoglobulin E; OCS, oral corticosteroid; PBE, peripheral blood eosinophil count; PBN, peripheral blood neutrophil count. Data are expressed as number (percentage) or median (interquartile). P values are from the Kruskal–Wallis test across Parts A–C. * p < 0.05 (vs PBE<300 & sputum eos <3%) ; # p < 0.05 (vs PBE<300 & sputum eos ≥3%).

Table S5. Biologic utilization and 12-month clinical remission across systemic–airway eosinophil discordance subclasses (Parts A–C).

	Part A (n=37)	Part B (n=9)	Part C (n=16)
Biologics-treated, n, (%)	28 (75.7)	7 (77.8)	7 (43.8)
Anti-IgE, n (%)	2 (7.1)	2 (28.6)	3 (42.9)
Anti-IL-5/R, n (%)	14 (50.0)	1 (14.3)	2 (28.6)
Anti-IL-4R, n (%)	12 (42.9)	4 (57.1)	2 (28.6)
Clinical remission among biologics-treated, n (%)	14 (50.0)	3 (42.9)	1 (14.3)
Clinical remission among all patients in each part, n (%)	14 (37.8)	3 (33.3)	1 (6.3)

Table S6. Baseline characteristics of anti- IL-5/R-treated versus anti-IL-4R-treated patients

	Anti-IL-5/R (n=17)	Anti-IL-4R (n=21)	P value
Age (years)	62 (48.5-66.5)	55 (48.5-66.5)	0.39
Women, n (%)	7 (41.2%)	9 (47.4%)	0.33
BMI (kg/m ²)	22.5 (20.6-24)	23.8 (20.1-25.7)	0.5
Non-smoker, n (%)	10 (58.8%)	16 (76.2%)	0.25
Disease duration (years)	15 (12.5-24)	17 (10.5-23)	0.95
PBE (/μL)	888.8 (479.6-1211.5)	508.2 (266-865.1)	0.09
PBN (/μL)	4480 (3095-6560)	3620 (3050-4075)	0.18
FeNO (ppb)	102 (33-170)	62 (34-110.5)	0.42
IgE (IU/mL)	497 (68.2-1680)	273 (50.9-730.5)	0.12
%FEV ₁	81.4 (59-92.1)	85 (62.7-97.1)	0.65
Severe disease, n (%)	17 (100%)	19 (90.5%)	0.19
mOCS, n (%)	8 (47.1%)	1 (4.8%)	0.002
ICS (μg/day; equivalent to fluticasone)	800 (500-800)	800 (775-1000)	0.02
Sputum eosinophil (%)	62.9 (20.6-77.2)	14 (3.8-56.4)	0.04
Sputum neutrophil (%)	28.1 (9.3-62.8)	55 (14.7-77.5)	0.23
ECP (ng/mL)	1492.5 (325.4-1977)	878.9 (188.2-1712.8)	0.25
Tryptase (pg/mL)	108 (9.7-242.6)	16.7 (3.9-177.8)	0.4
YKL-40 (ng/mL)	59 (22.4-87.8)	60.8 (30.6-130.1)	0.8
IL-6 (pg/mL)	39.9 (23.8-91.8)	69.7 (22.2-368)	0.21
IL-18 (pg/mL)	56.7 (8.8-255.5)	64.5 (12.2-141.3)	0.98

BMI, body mass index; ECP, eosinophil cationic protein; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; IgE, immunoglobulin E; OCS, oral corticosteroid; PBE, peripheral blood eosinophil count; PBN, peripheral blood neutrophil count. Data are expressed as number (percentage) or median (interquartile).

Table S7. Clinical characteristics in patients with or without clinical remission under anti-IL-4R α after exclusion of patients with EGPA, ABPA(M) and COPD

	Remission (n=12)	Non-Remission (n=8)	p value
Age (years)	56 (48.3-64.8)	50.5 (35.8-66.8)	0.56
Women, n (%)	6 (50%)	3 (37.5%)	0.67
BMI (kg/m ²)	23.6 (20.6-25.4)	24.1 (19.4-26.3)	0.85
Non-smoker, n (%)	8 (66.7%)	7 (87.5%)	0.60
Disease duration (years)	15 (9.8-28.3)	17 (9-23)	0.96
PBE (/μL)	529.0 (231.8-826.2)	437.4 (267.6-1082)	0.97
PBN (/μL)	3620 (3268-3980)	3635 (2555-5125)	0.90
FeNO (ppb)	83.5 (52.2-195.3)	41.5 (29-67.3)	0.03
IgE (IU/mL)	263.0 (30.9-955.5)	254.5 (56.8-533.8)	0.91
%FEV ₁	86.7 (82.3-97.8)	72.3 (51.2-96.7)	0.27
Severe disease, n (%)	11 (91.7%)	7 (87.5%)	1.00
mOCS, n (%)	1 (8.3)	0 (0.0)	1.00
ICS (μg/day; equivalent to fluticasone)	800 (762.5-950)	800 (575-1000)	0.83
Sputum eosinophil (%)	18.8 (2.9-60.9)	18.9 (3.3-61.0)	0.99
Sputum neutrophil (%)	59.6 (16.5-89.5)	30.9 (11.6-66.3)	0.31
ECP (ng/mL)	1503.0 (195.7-1779.2)	667.5 (179.5-1599.0)	0.52
Tryptase (pg/mL)	36.7 (4.6-285.5)	63.2 (2.5-141.0)	0.47
YKL-40 (ng/mL)	63.0 (34.9-216.8)	37.3 (0.3-78.0)	0.18
IL-6 (pg/mL)	213.8 (68.6-486.5)	19.4 (3.0-162.3)	0.02
IL-18 (pg/mL)	65.9 (30.3-218.1)	67.6 (10.5-144.8)	0.64

ABPA(M), Allergic Bronchopulmonary Aspergillosis (Mycosis); BMI, body mass index; ECP, eosinophil cationic protein; EGPA, Eosinophilic Granulomatosis with polyangiitis; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; IgE, immunoglobulin E; OCS, oral corticosteroid; PBE, peripheral blood eosinophil count; PBN, peripheral blood neutrophil count. Data are expressed as number (percentage) or median (interquartile),

Table S8: Exploratory logistic regression analyses for clinical remission

Univariate analysis			
	OR	95% CI	p value
Sputum IL-6 (log)	6.46	1.54-57.65	0.033
FeNO (Log)	52.02	1.77-9914.13	0.061
Multivariate analysis			
	OR	95% CI	p value
Sputum IL-6 (log)	4.49	1.04-38.22	0.043
FeNO (Log)	22.76	0.55-5691.96	0.108

OR, odd ratio; CI, confidence interval.