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CASE SERIES

Combining Dual Biologics Therapy for Severe Asthma: A Series of Ten Cases

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Background: Biologic therapy has revolutionized the management of severe asthma, but a subset of patients with severe asthma exhibits symptoms inadequately controlled by monotherapy, potentially due to the involvement of multi-type 2 pathways. Dual biologic therapy has emerged as a promising strategy, but its efficacy and safety are not yet fully understood.

Objective: To describe the characteristics, endotyping features, decision-making process and therapeutic response of patients with severe asthma on dual biologic therapy in a real-world setting.

Methods: We present ten patients on dual biologics for severe asthma. The biologic combinations include mepolizumab+ dupilumab (n=7), benralizumab+dupilumab (n=1), omazulab+mepolizumab (n=2). Therapeutic response was assessed by type 2 inflammation biomarkers, symptom control, frequency of acute exacerbations, daily oral corticosteroid (OCS) dosage and side effects.

Results: In our 10 cases, six of them are women, the mean age was 56±15 years old. The mean duration of combination therapy use was 13.5 months (range from 4 to 36 months). Dual biologic therapy was initiated because of inadequate asthma control (N1, N2, N6), poor control of comorbidities (N5, N7, N8, N9) or anti-IL4/13R-induced hypereosinophilia (N3, N4, N5, N7, N10) when treated with a single biologic agent. All ten patients exhibited good tolerance to the combined biologic therapies, leading to improvements in asthma and comorbidity management, and a reduction in OCS usage. No serious adverse events were reported.

Conclusion: Dual biologics have been shown to be both effective and safe. However, more studies are needed to fully assess the long-term benefits and potential risks of different combinations of biologic treatments.

Keywords: severe asthma, biologic therapy, dual therapy, combination therapy, monoclonal antibody

Introduction

Biologics have been a revolution in the treatment of severe asthma. To date, five biologic treatment options have been approved for the treatment of uncontrolled severe asthma and other type 2 inflammatory diseases, including anti-immunoglobulin E (IgE) (omalizumab), anti-interleukin-5 (IL-5; mepolizumab and reslizumab), IL-5 receptor alpha antagonists (IL-5R; benralizumab), anti-IL-4/IL-13 receptor-alpha (IL-4R; dupilumab), and anti-thymic stromal lymphopoietin (TSLP) (tezepelumab).[1] Currently, there is no universally accepted clinical practice guidance for the use of biologic agents. The GINA 2022 guidelines recommend assessing the efficacy of biologic agents at least four months after initiation, with the evaluation period potentially extended to 6–12 months if efficacy remains uncertain.[2] Primary criteria such as exacerbation rate, reduction in oral corticosteroid (OCS) dose, validated symptom measures (eg Asthma Control Test, ACT), lung function and biomarker assessment should be evaluated to guide adjustment of treatment strategies.[3] If a biologic agent proves ineffective, switching to another suitable biologic agent is recommended. If the response is partial, extending the duration of treatment or combination therapy may be appropriate.[4] It is noteworthy that a certain proportion of patients still experience

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only partial control of their symptoms despite receiving an appropriate single biological therapy.[5] Given the complex interplay of multiple type 2 inflammatory pathways, combination therapy should be considered as a potential strategy.[6,7] Preliminary data on combination therapy are limited, mostly from observational studies and case reports.[8,9] Dual biologic agents had been prescribed for several reasons: (1) Inadequately controlled asthma symptoms:[10,11] Patients with uncontrolled allergic and eosinophilic asthma phenotypes who do not respond adequately to either omalizumab or IL-5/IL-5R antagonists alone may benefit from combined biologic therapy. This combination typically includes anti-IgE (omalizumab) and anti-IL-5/IL-5 receptor antagonists (such as mepolizumab, reslizumab, or benralizumab). (2) Poor control of type 2 comorbidities:[11,12] For patients with severe asthma and uncontrolled T2-comorbidities, the combination of two biologics targeting different T2 pathways may provide additional improvement. Combination strategies include mepolizumab or benralizumab+dupilumab for chronic rhinosinusitis with nasal polyps (CRSwNP), omalizumab+mepolizumab for chronic spontaneous urticaria (CSU), and mepolizumab or benralizumab+dupilumab for atopic dermatitis (AD) et al. (3) Anti-IL-4/13R-induced hypereosinophilia:[8,13] Some patients initially achieve good control with dupilumab but experienced symptom recurrence due to elevated eosinophils levels induced by the treatment. The combination of dupilumab and mepolizumab has been shown to maintenance of symptoms control and normalize blood eosinophil levels.

Taken together, combination therapy with dual biologics may be an effective approach for patients whose symptoms remain partially controlled after the appropriate administration of single biologic agent.[8,11,14] However, more robust data are needed to refine treatment strategies for dual biologic therapy. This report details our experience with ten cases of dual biologic therapy, exploring clinical characteristics, endotypic features and decision-making process, which provides useful insights for developing effective clinical strategies for dual biologic therapy in future studies.

Materials and Methods

This is a retrospective case series of 10 patients with severe eosinophilic asthma who, despite receiving optimal treatment with medium to high doses of inhaled corticosteroids (ICS) and up to two additional controllers, including long-acting beta-agonist (LABA), long-acting antimuscarinic antagonist (LAMA), montelukast and OCS, failed to achieve good symptom control and experienced frequent acute exacerbations. Reversible factors such as persistent allergen exposure, poor adherence, and inadequate inhaler technique were addressed. For each patient, we describe clinical characteristics, endotypic features, decision making process, clinical parameters and biomarkers at baseline and after dual biologic treatment. The study was approved by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (Ethics registration number ES-2023-114-01) and all of the patients provided written informed consent for their case details to be published.

Results

The demographics and objective measurements are summarized in Table 1. Details for each patient are provided below.

Case 1

An 80-year-old man was diagnosed 20 years ago with non-allergic severe eosinophilic asthma (SEA), allergic rhinitis (AR), and chronic obstructive pulmonary disease (COPD). Despite maximal therapy with a high-dose of ICS, LABA +LAMA and montelukast (10 mg/day), he experienced recurrent acute exacerbations (3 times in the last year), requiring systemic corticosteroids and hospitalization. While on systemic corticosteroids (methylprednisolone 40 mg/day), his ACT score was 16, with blood eosinophil count (BEC) level of 490 cells/ul, sputum eosinophil count (SEC) level of 67%, fractional exhaled nitric oxide (FeNO) level of 60 ppb and total immunoglobulin E (tIgE) of 272.8 IU/mL (specific immunoglobulin E (sIgE) was negative), forced expiratory volume in 1 second (FEV1) was 1.39 L (forced expiratory volume in 1 second% predicted, FEV1%pre of 59.6%). Given his advanced age, the asthma-COPD overlap, severe airflow limitation, OCS dependence and frequency of exacerbations, he was initially recommended dupilumab. However, his family was concerned about a further increase in blood eosinophilia leading to relapse, so a combination of dupilumab (300 mg, q4w) and mepolizumab (100 mg, q4w) was considered. After dual biologic therapy, his condition improved significantly, with no further exacerbations and hospitalizations or the systemic corticosteroids administration, his ACT score was 25, with BEC level of 120 cells/ul, SEC level of 4.5%, FeNO level of 38 ppb and tIgE of 36.53 IU/mL without OCS, FEV1 was 1.58 L (FEV1%pre of 87.69%).

Table 1 Demographics and Clinical Characteristics of Patients at Baseline and After Dual Biologic

	All	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10
Baseline characteristics											
Age (y)	56±15	80	45	59	55	34	82	57	47	59	45
Female sex, n (%)	6 (60%)	M	M	F	F	F	F	M	M	F	F
Diagnosis	N/A	SEA	SEA	SEA	SEA	SEA	SEA	SEA	SEA	SEA	SEA
Comorbidities	N/A	AR, COPD	CRS, localized-EGPA	CRS, AD	EGPA, CRS, EOM	localized-EGPA, EOM, CRSwNP	CRS	localized-EGPA, CRS, EOM	AR, CSU	localized-EGPA, AR, CRS	EGPA, AR, CRS, CSU
Atopy, n (%)	6 (60%)	N	Y	Y	Y	Y	N	Y	N	N	Y
Biologics	N/A	Dupi+Mepo	Benra→Dupi→Dupi +Mepo	Dupi→Dupi +Mepo	Dupi→Mepo→Dupi +Mepo	Benra→Dupi→Dupi +Mepo	Mepo→Mepo +Dupi	Oma→Benra→Benra +Dupi	Oma→Oma +Mepo→Mepo	Oma→Oma +Mepo→Mepo	Oma→ Mepo→Dupi→Mepo +Dupi
Combined reason		advanced age, asthma-COPD overlap, severe airflow restriction, OCS dependence and exacerbations	CRW and respiratory function improved a little with Benra alone, switched to Dupi alone led to symptoms controlled and no exacerbations, but OCS still required 15–20mg/d	elevated blood eosinophils with Dupi	blood eosinophils elevated with Dupi alone, switched to Mepo alone led to CRS and EOM relapsed	CRW and EOM uncontrolled with Benra alone, switched to Dupi improved CRW and EMO, but led to exacerbation induced by significant increase in blood eosinophils	exacerbations still persist and OCS could not discontinue with Mepo alone	asthma symptom uncontrolled with Oma alone, CRS and EOM uncontrolled with Benra alone, Dupi induced elevated blood eosinophils	asthma symptom uncontrolled with Oma alone, reserve Oma for CUS, but urticaria repeated relapses	asthma symptom uncontrolled with Oma alone and resulted in blood eosinophils elevation	symptom uncontrolled with Oma or Mepo alone, elevated blood eosinophils and diagnosis EGPA with Dupi
Combined benefits		no exacerbations, no OCS and symptoms controlled	Symptoms good controlled and OCS reduced to 5–10 mg/d	no nasal inhalers, no ICS+LABA, achieved clinical remission	Asthma, CRS and EOM controlled, and blood eosinophils not elevated	Asthma, CRS and EOM controlled, and blood eosinophils not elevated	Symptoms controlled, no exacerbations and OCS discontinued	CRS and EOM controlled and blood eosinophils not elevated	discontinuation of Oma and mepo alone did not result in relapse	discontinuation of Oma and mepo alone did not result in relapse	Symptoms controlled and blood eosinophils not elevated
BEC (cells/ul)											
Before dual biologics	968 (110–2460)	490	1000	1100	320	1740	110	730	1130	600	2460
After dual biologics	189 (70–530)	120	150	70	80	150	530	0	100	340	350
SEC, %											
Before dual biologics	34.5 (6.5–67)	67	8.5	6.5	26	33	49	36	59.5	7.5	52.5
After dual biologics	6.75 (1–20.5)	4.5	5.75	2	20.5	-	12	0	1	1	14

(*Continued*)

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Table 1 (Continued).

	All	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10
FeNO (ppb)											
Before dual biologics	71 (34–134)	60	83	34	56	55	91	56	103	43	134
After dual biologics	28.9 (13–48)	38	48	44	13	20	21	27	20	15	43
IgE (IU/mL)											
Before dual biologics	772 (120–1620)	272.8	388	120	1112	288	248	1620	231.79	1519	1922
After dual biologics	158 (33.3–432.5)	36.53	197	33.3	151	-	423	65.6	71.54	432.5	15.06
FEV_1 (L)											
Before dual biologics	1.89±0.68	1.39	1.44	1.54	1.89	2.86	0.71	2.04	2.94	2.33	1.83
After dual biologics	2.15±0.82	1.58	1.16	2.24	2.58	2.92	0.85	2.09	3.69	2.15	2.29
ACT											
Before dual biologics	17±2	16	16	15	18	20	15	19	15	20	19
After dual biologics	24±1	25	24	25	24	25	24	22	23	25	25
SNOT-22											
Before dual biologics	52±12	-	51	55	60	65	-	65	30	42	52
After dual biologics	20±15	-	8	10	25	9	10	52	24	28	10
Exacerbations (/year)											
Before dual biologics	2.1±0.73	3	3	1	1	2	2	3	2	2	2
After dual biologics	0	0	0	0	0	0	0	0	0	0	0

OCS does (mg/d)											
Before dual biologics	20(10–30)	30	30	20	10	20	10	15	30	20	20
After dual biologics	1(0–10)	0	5	0	0	0	0	0	5	0	0
Months of combination biologic	13.5±8.6	8	14	15	11	13	15	36	11	8	4
Side effects	0 (100%)	N	N	N	N	N	N	N	N	N	N

Abbreviations: AR, allergic rhinitis; AD, atopic dermatitis; BEC, blood eosinophil count; COPD, chronic obstructive pulmonary disease; CSU, chronic spontaneous urticaria; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyp; EGPA,eosinophilic granulomatosis with polyangiitis; EOM, Eosinophilic otitis media; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; q4w, every 4 weeks; SEA, severe eosinophilic asthma; SEC: sputum eosinophil count; OCS, oral corticosteroid; N, no; N/A, not available; Y, yes. Benra, benralizumab; Dupi, dupilumab; Mepo, mepolizumab; Oma, Omalizumab.

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Case 2

A 45-year-old man with allergic SEA, chronic rhinosinusitis without nasal polyps (CRSsNP) and localized-eosinophilic granulomatous vasculitis (EGPA) had uncontrolled asthma symptoms on high-dose ICS+LABA+LAMA and montelukast (10 mg/day). Prednisone (30 mg/day) and methotrexate (20 mg once/week) provided temporary relief, but symptoms recurred with OCS tapering, correlating with elevated blood eosinophil peaking at 3420 cells/ul. Benralizumab, initiated in December 2019, stopped further exacerbations and reduced OCS to 20 mg/day, but did not improve respiratory function or nasal symptoms. Dupilumab replaced benralizumab in January 2021, with resolution of nasal symptoms, no asthma exacerbations, and improved sinus CT, with a slight improvement in FEV1. OCS reduction stalled at 15–20 mg/day. At that time, his ACT score was 16 and Sino-Nasal Outcome Test-22 (SNOT-22) was 51, with BEC level of 1000 cell/ul, SEC level of 8.5%, FeNO level of 83 ppb and tIgE of 388 IU/mL (aspergillus fumigatus allergen-sIgE was positive), FEV1 was 1.44 L (FEV1%pre of 40%). To further reduce the dose of OCS, mepolizumab was added to dupilumab in 2023. This combination allowed further reduction of OCS to 5–10 mg/day without exacerbations, but improvement in FEV1 remained minimal. After dual biologic therapy, his ACT score was 24 and SNOT-22 was 8, with BEC level of 150 cells/ul, SEC level of 5.75%, FeNO level of 48 ppb and tIgE of 197 IU/mL, FEV1 was 1.16 L (FEV1%pre of 33.2%).

Case 3

A 59-year-old woman with allergic late-onset SEA, CRSsNP, and atopic dermatitis (AD), poorly controlled on ICS+LABA +LAMA, montelukast (10 mg/day) and OCS (prednisone 20 mg/day), was started on dupilumab (300 mg, q2w) in August 2021, which improved her asthma symptoms and allowed OCS to be discontinued. However, after one month of treatment, her blood eosinophils gradually increased, with monthly tests consistently showing levels above 1500 cells/ul, peaking at 2460 cells/ul (25.4%). After excluding other potential causes, dupilumab is suspected to be the cause of the hypereosinophilia. At that time, her ACT score was 15 and SNOT-22 score was 55, with BEC level of 1100 cells/ul, SEC level of 6.5%, FeNO level of 34 ppb and tIgE of 120 IU/mL (inhalant allergen-sIgE was positive). She had occasional mild asthma attacks and FEV1 decreased to 1.54L (FEV1%pre of 70.3%). In combination with mepolizumab (initially 300 mg, q4w, then reduced to 100 mg, q4w for economic reason) from March 2023, the eosinophil levels normalized by May 2023. The patient achieved clinical remission, with stable asthma, improved CRSsNP and AD, and discontinued nasal corticosteroids, ICS, and OCS. After dual therapy, her ACT score was 25 and SNOT-22 score was 10, with BEC level of 70 cells/ul, SEC level of 2%, FeNO level of 44 ppb and tIgE of 33.3 IU/mL, FEV1 increased to 2.24 L (FEV1%pre of 99.4%).

Case 4

A 55-year-old woman presented with late-onset allergic SEA, localized-EGPA, CRSsNP and eosinophilic otitis media (EOM) continued to suffer from persistent asthma, nasal and ear discomfort symptoms despite maximal therapy with ICS +LABA+LAMA, montelukast (10 mg/day), OCS (prednisolone 5–15mg/day) and immunosuppressants (cyclophosphamide 50mg/day). In November 2020, dupilumab (300 mg, q2w) was initiated, resulting in marked improvement in nasal and ear symptoms, allowing rapid discontinuation of immunosuppressants and reduction of OCS to 5–10 mg/day, but not complete withdrawal. Blood eosinophils were 1360 cells/ul (19.2%) in August 2022 and 1340 cells/ul (10.3%) in May 2023. Mepolizumab (100 mg, q4w) replaced dupilumab in June 2023, but nasal and ear symptoms worsened two months later. At that time, her ACT score was 18 and SNOT-22 score was 60, with BEC level of 320 cells/ul, SEC level of 26%, FeNO level of 56 ppb, tIgE of 1112 IU/mL (dust mite allergen-sIgE was positive) and FEV1 of 1.89L (FEV1% pre of 97.7%). Since June 2023, the combination of dupilumab (300 mg, q4w) and mepolizumab (100 mg, q4w) relieved her CRS and EOM symptoms, discontinued OCS, normalized blood eosinophil levels and achieved an ACT score of 24, SNOT-22 score of 25 without side effects. Her BEC level was 80 cells/ul, SEC level was 20.5%, FeNO level was 13 ppb, tIgE was 151 IU/mL and FEV1 increased to 2.58 L (FEV1%pre 107.8%).

Case 5

A 34-year-old woman with late-onset allergic SEA, localized-EGPA, EOM, and chronic rhinosinusitis with nasal polyps (CRSwNP) experienced frequent exacerbations under maximal treatment with high-dose ICS+LABA+LAMA,

montelukast (10mg/day), OCS (methylprednisolone 8–24mg/day) and immunosuppressants (mycophenolate mofetil and methotrexate). In 2019, benralizumab was administered for one year, achieving asthma control but no improvement in CRSwNP and EOM, and was discontinued due to cost (Benralizumab was excluded from insurance coverage in China at that time). In November 2021, dupilumab was started (initially 600 mg, followed by 300 mg, q2w), which improved CRSwNP and EOM. However, blood eosinophil levels fluctuated significantly for four months after starting dupilumab (1260–880-1700-690-1610 cells/ul). The patient had two asthma exacerbations requiring intravenous corticosteroids. In May 2023, her ACT score was 20 and SNOT-22 score was 65, with BEC level of 1740 cells/ul, SEC level of 33%, FeNO level of 55 ppb, tIgE of 288 IU/mL (food allergen-sIgE was positive) and FEV1 was 2.86L (FEV1%pre 93.3%). Given her elevated blood eosinophil level of 27.1% (2540 cells/ul), she was started on mepolizumab (100 mg, q4w) in combination with dupilumab (300 mg, q4w). One week later, her blood eosinophil count fell to 130 cells/ul, and her condition began to stabilize, allowing the OCS to be tapered. One year later, she achieved significant improvement in CRSwNP and EOM, recovery of olfactory sensation, discontinuation of OCS and well-controlled asthma. After dual therapy, her ACT score was 25 and SNOT-22 score was 9, with BEC level of 150 cells/ul, FeNO level of 20 ppb and FEV1 was 2.92 L (FEV1%pre of 99.6%).

Case 6

An 82-year-old woman with non-allergic SEA and CRSsNP experienced recurrent asthma symptoms with high-dose ICS +LABA+LAMA, montelukast (10mg/day) and OCS (prednisolone 10–15mg/day). Mepolizumab (100 mg, q4w) was added but resulted in only mild improvement and a reduction in OCS (prednisolone 10mg/day). She was hospitalized twice for exacerbations in January 2023 and April 2023. At that time, her ACT score was 15 with BEC level of 110 cells/ul, SEC level of 49%, FeNO level of 91ppb, tIgE of 248IU/mL (sIgE was negative) and FEV1 of 0.71L (FEV1%pre of 46.97%). Given her advantage age, long-term dependence on OCS (prednisolone 10mg/day) and the limited benefit of mepolizumab alone, dupilumab (300 mg, q4w) was added. After one year on the dual biologics, she discontinued OCS and achieved complete symptom control of asthma and nasal symptoms without OCS and exacerbations. Her ACT score was 24 and SNOT-22 score was 10, with BEC level of 530 cells/ul, SEC level of 12%, FeNO level of 21 ppb, tIgE of 423 IU/mL and FEV1 was 0.85L (FEV1%pre of 53.69%).

Case 7

A 57-year-old man with allergic SEA, localized-EGPA, CRSsNP and EOM had refractory asthma symptoms despite high-dose ICS+LABA+LAMA, immunosuppressants (sequential use of cyclophosphamide, cyclosporine, mycophenolate mofetil and methotrexate), montelukast (10mg/day) and OCS-dependent (prednisolone 5–25mg/day). To effectively control the disease, biologic therapy was started. Four courses of omalizumab (600 mg, q4w) failed to control symptoms and reduce the need for OCS. Switching to benralizumab (30 mg, q2w) improved asthma control, allowed discontinuation of immunosuppressants and reduced OCS to 10–15 mg/day. However, he continued to experience nasal and ear discomfort. At that time, his ACT score was 19 and SNOT-22 score was 65, with BEC level of 730 cells/ul, SEC level of 36%, FeNO level of 56 ppb, tIgE of 1620 IU/mL (penicillium and dust mite allergen-sIgE was positive) and FEV1 of 2.04L (FEV1%pre of 63%). The addition of dupilumab (600 mg, q4w) improved control of CRW and EOM. As benralizumab and dupilumab were expensive and not covered by insurance, patients hope to achieve basic asthma management with minimal use of biologics to reduce the financial burden. In January 2022, we tried to extend the interval of benralizumab use. Initially, the patient showed good symptom control and low blood eosinophil levels in the second month. However, four months after stopping benralizumab, the patient began to experience an exacerbation requiring OCS (prednisolone 15–20mg/day), accompanied by an increase in blood eosinophilia. Interestingly, all three episodes of exacerbation occurred four months after the last dose of benralizumab administration and were accompanied by elevated blood eosinophilia, but blood eosinophilia was normal in the second month after stopping benralizumab. Treatment adjustment to benralizumab (30 mg, q12w) and dupilumab (300 mg, q6w) effectively controlled symptoms, achieving a BEC level of 0%, an ACT score of 23 and a SNOT-22 score of 28. In November 2023, following a BEC level of 1240 cells/μL (16.7%) at 14 weeks post-benralizumab, dupilumab was discontinued. In February 2024, due to worsening CRSsNP and EOM, dupilumab (300 mg, q4w) was reintroduced with benralizumab (30 mg, q8w), stabilizing

the patient's condition until August this year. His ACT score was 22 and SNOT-22 score was 52, with BEC level of 0 cells/ul, SEC level of 0%, FeNO level of 27ppb, tIgE of 65.6IU/mL and FEV1 was 2.09L (FEV1%pre of 67.2%).

Case 8

A 47-year-old man, diagnosed with SEA, CRSsNP and chronic spontaneous urticaria (CSU), experienced recurrent exacerbations despite maximal therapy with high-dose ICS+LABA+LAMA, montelukast (10mg/day), and remained dependent on OCS (prednisolone 20–30mg/day). After one year of treatment with omalizumab (150 mg, q4w), his asthma symptoms showed no significant improvement. At that time, his ACT score was 15 and SNOT-22 score was 30, with BEC level of 1130 cells/ul, SEC level of 59.5%, FeNO level of 103 ppb, tIgE 231.79 IU/mL (sIgE was negative) and FEV1 of 2.94L (FEV1%pre of 71.75%). Considering that omalizumab is potentially effective for CSU and is covered by insurance, he was started on combination therapy with mepolizumab (200 mg, q4w) and omalizumab (150 mg, q4w) in April 2023. This treatment effectively controlled his asthma symptoms, but the urticaria persisted and a skin biopsy showed the presence of occasional eosinophils around small blood vessels in the subcutaneous tissue. Due to the suboptimal control of urticaria with omalizumab, it was discontinued after March 2024. The patient is now on monotherapy with mepolizumab (200 mg, q4w), with stable symptoms of asthma and urticaria. His ACT score was 23 and SNOT-22 score was 24, with BEC level of 100 cells/ul, SEC level of 1%, FeNO level of 15 ppb, tIgE of 71.54 IU/mL and FEV1 was 3.69L (FEV1%pre of 89.91%).

Case 9

A 59-year-old woman with non-allergic SEA and CRSsNP in 2018. She required high-dose ICS+LABA+LAMA, montelukast (10mg/day) and OCS-dependent (prednisolone 10-20mg/day) to control her symptoms. In 2021, biologic agents were considered to reduce the adverse effects of OCS. However, at that time, only omalizumab and dupilumab were available in China, and dupilumab was not covered by insurance for asthma treatment. As her total IgE was 1519 IU/mL, omalizumab (600 mg, q4w) was initiated despite a negative sIgE test. However, her blood eosinophil counts gradually increased (280–470-600-640-940 cells/ul), peaking at 1240 cells/ul (16.8%) after 10 courses. The patient's cough worsened, with an ACT score of 20 and SNOT-22 score of 42, BEC level of 600 cells/ul, SEC level of 7.5%, FeNO level of 43 ppb, tIgE of 1519 IU/mL (sIgE was negative) and FEV1 was 2.33L (FEV1%pre of 109.3%). Given that omalizumab partially controlled her symptoms but eosinophil levels were rising, and considering that omalizumab was covered by the insurance, dual therapy with omalizumab and mepolizumab (100 mg, q4w) was initiated, resulting in a significant reduction in blood eosinophils. After 8 courses of dual biologics, she was tried on mepolizumab monotherapy (200 mg, q4w). To date, eight courses of monotherapy has been administered, her symptoms are well controlled with ICS+LABA alone. Her ACT score was 25 and SNOT-22 score was 28, with BEC level of 340 cells/ul, SEC level of 1%, FeNO level of 15 ppb, tIgE of 432.5 IU/mL and FEV1 was 2.15L (FEV1%pre of 99.91%).

Case 10

A 45-year-old woman with allergic SEA, EGPA, AR, CRSsNP and CSU, failed to achieve symptom control despite receiving maximal inhaled therapy. Additional treatment with montelukast (10mg/day) and OCS (prednisolone 10–20mg/day) also failed to achieve good control. She was prescribed omalizumab (600 mg, q4w) to manage her symptoms but continued to experience recurrent wheals, uncontrolled asthma symptoms (ACT score of 19 and SNOT-22 score of 52) along with elevated BEC level at 2460 cells/ul, SEC level of 52.5%, FeNO level of 134 ppb, tIgE 1922 IU/mL (dust mite allergen-sIgE was positive) and a reduced FEV1 was 1.83 L(FEV1%pre of 65.96%). After 5 months, her treatment was changed from omalizumab to mepolizumab (100 mg, q4w), CRSsNP and FEV1 still showed no obvious improvement. The regimen was changed to dupilumab (300 mg, q4w), which resulted in a significant improvement in her asthma symptoms, CRSsNP, and lung function. However, her blood eosinophil counts gradually increased during dupilumab therapy (2200–2900-2200-3800-2640 cells/ul), and eosinophilic infiltration in the bronchial mucosa and distal ileum (103 cells/HP) was detected, which was diagnosed as EGPA. As a result, the combination of mepolizumab (200 mg, q4w) and dupilumab (300 mg, q4w) successfully improved her multiple symptom control and quality of life. After dual therapy, her ACT score was 25 and SNOT-22 score was 10, with BEC level of 350 cells/ul, SEC level of 14%, FeNO level of 43 ppb, tIgE of 15.06 IU/mL and FEV1 was 2.29L (FEV1%pre of 84%).

Discussion

This case series details the successful management of ten patients with SEA and T2 comorbidities using dual biological agents. Patients who did not respond adequately to single biologic therapy were switched to combination treatment, which effectively controlled asthma symptoms, reduced acute exacerbations, and allowed the reduction or discontinuation of OCS without significant adverse effects.[4]

Patient N1, with advanced age, asthma-COPD overlap, severe airflow limitation, frequent exacerbations were dependent on OCS. Despite systemic corticosteroid treatment, the BEC remains elevated at 500 cells/ul. His family was concerned about the potential for further increases in blood eosinophilia leading to relapse, he was initially treated with a combination of dupilumab and mepolizumab. Patients N2, N5, N6, and N7 initiated combination therapy due to inadequate asthma control (N6), poor control of comorbidities (N5, N7), or inability to reduce OCS (N2). The combination of anti-IL-5/IL-5R and dupilumab was frequently used.[7] Patients N3, N4, N5, N7 and N10 who experienced a significant increase in blood eosinophil levels following the dupilumab, achieved effective control with the addition of anti-IL-5 or IL-5R. Notably, patient N7's good control with the combination of benralizumab and dupilumab was compromised when the benralizumab interval exceeded two months due to elevated blood eosinophil levels and acute exacerbations, suggesting that the optimal dosing frequency for dual biologics should be further investigated. Inadequate control of CRSsNP/CRSwNP and EOM was often observed with single anti-IL-5/IL-5R monotherapy,[11,12,15] whether initially prescribed anti-IL-5/IL-5R (N2, N5, N7, N10), switched from anti-IL-4R to anti-IL-5/IL-5R (N4, N7), or after discontinuation of anti-IL-4R following combination therapy with anti-IL-5/IL-5R (N4, N7), suggesting a beneficial effect of anti-IL-4R on these conditions. Patient N8, with non-allergic SEA and CSU, had recurrent exacerbations, persistent dermatological symptoms, and continued dependence on OCS despite omalizumab therapy. The addition of an anti-IL-5 agent resulted in well-controlled asthma symptoms, but persistent skin eruptions. Importantly, discontinuation of omalizumab did not result in asthma flare-ups, or worsening of urticaria. This case suggests that omalizumab may not be sufficient to treat CSU when eosinophilia is elevated. In patient N9, anti-IL-5 therapy was added due to persistent blood eosinophilia during omalizumab treatment, and the subsequent withdrawal of omalizumab did not lead to asthma relapse, consistent with the observations by Chapman et al.[16] This suggests that the combination and withdrawal of biologic agents should be evaluated dynamically. Although most reports indicate that combination biologic therapy can achieve good asthma control, some patients still fail to achieve complete control with combination therapy, possibly due to non-T2 inflammatory components.[12,14] Patient selection and efficacy evaluation of combination biologic therapy deserve further consideration.

Severe asthma is a complex disease driven by distinct types of inflammatory process. Biologic agents, which target specific molecules and inflammatory pathways, have provided valuable insights into the strategy for severe asthma monoclonal, but clinical response vary widely.[17] Omalizumab is a recombinant humanized anti-IgE antibody that selectively binds to high affinity Fc receptor of serum free IgE and prevents the IgE-mediated inflammatory cascade in response to allergic antigenic stimuli. Omalizumab has shown significant efficacy in the treatment of early-onset allergic asthma in adolescents.[18] However, its efficacy is significantly reduced in adult patients with chronic severe allergic asthma, with asthma exacerbation rates reduced by only 25%.[19] An open-label study has shown that in patients with severe eosinophilic asthma who are eligible for both omalizumab and mepolizumab, switching to mepolizumab when omalizumab treatment is inadequate can effectively improve their asthma control.[16] In our study, omalizumab was initially used because of the need to manage comorbidities of CSU (N8) or limitation in drug accessibility (N9). However, asthma control was not adequate with omalizumab alone. The combination of omalizumab and mepolizumab achieved good asthma control and withdrawal of omalizumab did not lead to recurrence of symptoms. This finding is consistent with the previous study.[16] Anti-IL-5/IL-5 receptor antagonists (such as mepolizumab, reslizumab, or benralizumab), which target IL-5 or its receptor IL-5Ralpha, inhibit the proliferation and activation of eosinophils and are approved for use in patients with severe eosinophilic asthma. Studies have demonstrated that they can effectively improve patient's symptoms, reduce acute exacerbations and decrease the use of systemic corticosteroids[20,21]. However, the improvement in lung function varies among individuals.[22] Dupilumab is an IL-4 receptor alpha monoclonal antibody that binds to the shared IL-4 receptor alpha of IL-4 and IL-13, which blocks both IL-4 and IL-13 signaling. It has been approved for moderate-to-severe AD, moderate-to-severe eosinophilic or OCS-dependent asthma, inadequately controlled CRSwNP and COPD with T2 inflammation. By blocking the migration of eosinophils into tissues, dupilumab

could induce a transient increase in eosinophils, which has been reported to induce EGPA.[23,24] In our study, patients (N2, N5, N6, N7, N10) experienced inadequate control of asthma or comorbidity symptoms, difficulty reducing OCS use, or mild improvement in lung function when treated with anti-IL-5/IL-5R therapy alone. Although dupilumab improved their symptoms and lung function significantly, it also caused elevated eosinophil levels, which led to recurrent symptoms. The dual therapy of anti-IL5/IL-5R and dupilumab enabled the patients to achieve satisfactory therapeutic outcomes. This finding is consistent with current studies showing that dupilumab is more effective than other T2 biologics in improving CRSwNP[25] and significantly superior to anti-IL-5 biologics in improving FEV1.[26] In addition, switching from other biologics to dupliuzumab can further improve lung function with CRSwNP.[25]

Safety is an important factor that need to be consider in combination biologic therapy. To date, no serious side effects have been reported with combination biologic therapies.[8,14] Our cases, treated with dual biologics for 7 to 14 months without additional washout periods, also showed no increased risk of infection, autoimmune disease, or tumor development.

The high cost of dual biologics therapy is also an important factor to be taken into account. It is estimated that the annual cost of dual biologic therapy ranges from $ 60,000 to $ 80,000.[27] While this cost may be partially offset by a reduction in repeated hospitalizations and improved productivity, it remains a significant financial burden, particularly in low-resource settings. Therefore, careful patient selection and dynamic evaluation throughout the course of treatment are essential to maximize the potential benefits of dual biologic therapy while ensuring cost-effectiveness.

Certainly, the current study has some limitations, such as a small sample size and lack of a control group, which may affect the generalizability of the results. Future research with larger, controlled studies is needed to confirm these findings and to further investigate the long-term efficacy and safety of dual biologic therapy.

In conclusion, dual biologics therapy offers an effective strategy for patients with SEA and comorbidities who are partially response or inadequately controlled on single biologic therapy. The choice of agents should be based on phenotype, safety, and cost-effectiveness to ensure precision medicine. Although our study's case number is limited, it provides valuable insights for future clinical trials and treatment strategies.

Abbreviation

ACT, Asthma Control Test; AD, atopic dermatitis; AR, allergic rhinitis; BEC, blood eosinophil count; COPD, chronic obstructive pulmonary disease; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; EGPA, eosinophilic granulomatous with polyangiitis; EOM, eosinophilic otitis media; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FEV1%pre, forced expiratory volume in 1 second% predicted; GINA, The Global Strategy for Asthma Management; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta-agonist; LAMA, long-acting antimuscarinic antagonist; OCS, oral corticosteroid; SEA, severe eosinophilic asthma; SEC, sputum eosinophil count; SNOT-22, Sino-Nasal Outcome Test-22; sIgE, specific immunoglobulin E; tIgE, total immunoglobulin E; TSLP, thymic stromal lymphopoietin.

Consent

All patients provided written informed consent for their case details to be published.

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Disclosure

The authors report no conflicts of interest in this work.

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