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Combining Biologics Targeting Eosinophils (IL-5/IL-5R), IgE, and IL-4/IL-13 in Allergic and Inflammatory Diseases

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ABSTRACT

The indications for biologic therapy are expanding. Patients may benefit from different biologics for separate conditions or one condition with multiple pathogenic mechanisms targeted by different biologics. We sought to determine the frequency and safety of combining biologics targeting IgE, IL-5, IL-5R, and IL-4/IL-13 in patients referred to a large academic health system through retrospective chart review. Between January 1, 2015 and July 31, 2021, 25 patients receiving multiple biologics simultaneously were identified. Combinations included omalizumab + mepolizumab (n = 11), omalizumab + dupilumab (n = 6), omalizumab + benralizumab (n = 4), mepolizumab + dupilumab (n = 3), and omalizumab + dupilumab + mepolizumab (n = 1). Sixteen patients were receiving multiple biologics for the same condition, most commonly asthma (n = 10). Nine patients were treated for separate conditions, with chronic spontaneous urticaria and atopic dermatitis being the most common combination (n = 3). The median duration of combination biologic use was 17.5 months. There were no reports of anaphylaxis, other allergic reaction, immune dysfunction, pneumonia, or development of malignancy. The use of multiple biologics appears to be well tolerated in this case series. Prospective study is needed to better determine the efficacy, safety, and cost-effectiveness of this approach.

Keywords: Biologic, Eosinophils, Omalizumab, Benralizumab, Mepolizumab, Dupilumab

To the Editor:

The indications for biologic therapy in allergic diseases are expanding. As this expansion continues, patients may benefit from different biologics for separate conditions, such as concomitant chronic spontaneous urticaria (CSU) and atopic dermatitis (AD). Alternatively, a patient may have one condition with multiple pathogenic mechanisms that may be targeted by biologics with separate targets. Asthma is a prime example with therapies targeting IgE (omalizumab), IL-5 (mepolizumab, benralizumab, reslizumab), IL-4/IL-13 (dupilumab), and thymic stromal lymphopoietin (TSLP) (tezepelumab) all approved in specific clinical situations. With patients and healthcare providers considering multiple biologic options, there is a paucity of data regarding the safety of combination biologic therapy. One prior case series reported ten patients with CSU plus an additional inflammatory condition that were treated with omalizumab and a biologic targeting tumor necrosis factor alpha or IL-17 for a duration of 3–12 months with no major adverse effects.[1] Other case reports describe 1 to 3 patients with either asthma or allergic bronchopulmonary aspergillosis (ABPA) treated with omalizumab and either mepolizumab,

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Patient	Age/ Sex	Biologic 1[a]	Biologic 2	Dose 1	Dose 2	Indication 1	Indication 2	Months between biologic initiation	Baseline AEC[b]	Baseline IgE[b]	Aeroallergen sensitivity[c]	Months of combination biologic use	Adverse Effects[d]
1	42F	Omalizumab	Dupilumab	300 mg q4w	300 mg q2w	CSU	AD	12	0.70	66	Yes	24	No
2	58 M	Omalizumab	Dupilumab	300 mg q4w	300 mg q2w	CSU	AD	12	Unknown	462	Yes[e]	3	No
3	42 M	Omalizumab	Dupilumab	375 mg q2w	300 mg q2w	ABPA	ABPA	6	0.95	1958	No	10	No
4	63F	Omalizumab	Dupilumab	125 mg q4w	300 mg q2w	CSU	CSU	3	0.74	Unknown	No	24	No
5	56F	Omalizumab	Dupilumab	300 mg q4w	300 mg q2w	Urticarial Dermatitis	Urticarial Dermatitis	4	0.20	Unknown	No	2	No
6	26F	Omalizumab	Dupilumab	150 mg q4w	300 mg q2w	CSU	AD	16	0.53	Unknown	Yes[e]	17	No
7	53F	Omalizumab	Benralizumab	300 mg q4w	30 mg q8w	Asthma	Asthma	Unknown	0.40	Unknown	No	Unknown	No
8	75F	Omalizumab	Benralizumab	300 mg q4w	30 mg q4w	Asthma	Asthma	Unknown	0.52	390	No	3	No
9	45F	Omalizumab	Benralizumab	150 mg q4w	30 mg q4w	Asthma	Asthma	Unknown	1.65	9296	Yes	36	No
10	27F	Omalizumab	Benralizumab	150 mg q4w	30 mg q4w	Asthma	Asthma	Unknown	0.90	8	No	12	No
11	54 M	Mepolizumab	Dupilumab	300 mg q4w	300 mg q2w	HES	AD	13	1.10	64	No	24	No
12	41F	Mepolizumab	Dupilumab	300 mg q4w	300 mg q2w	EGPA	CRSwNP	62	1.40	174	No	1	No
13	40 M	Mepolizumab	Dupilumab	100 mg q4w	300 mg q2w	Asthma	CRSwNP	62	0.40	35	No	15	No
14	52F	Omalizumab	Mepolizumab	Unknown	100 mg q4w	Asthma	EGPA	Unknown	0.46	1511	No	7	No
15	63F	Omalizumab	Mepolizumab	225 mg q4w	300 mg q4w	Asthma	Asthma	6	0.66	464	No	24	No
16	12F	Omalizumab	Mepolizumab	300 mg q4w	100 mg q4w	Asthma	Asthma	36	1.30	475	No	3	No
17	73F	Omalizumab	Mepolizumab	300 mg q4w	100 mg q4w	Asthma	Asthma	24	1.00	274	No	18	No
18	68 M	Omalizumab	Mepolizumab	375 mg q4w	100 mg q4w	ABPA	ABPA	16	0.70	1309	Yes	36	No

19	47F	Omalizumab	Mepolizumab	Unknown	100 mg q4w	CSU	Asthma	25	0.62	14	Yes	24	No
20	71 M	Omalizumab	Mepolizumab	300 mg q4w	100 mg q4w	Asthma	Asthma	72	Unknown	Unknown	No	36	No
21	63 M	Omalizumab	Mepolizumab	300 mg q4w	100 mg q4w	Asthma	Asthma	33	0.47	104	Yes	51	No
22	68 M	Omalizumab	Mepolizumab	375 mg q4w	100 mg q4w	ABPA	ABPA	10	0.50	1700	No	12	No
23	51 M	Omalizumab	Mepolizumab	300 mg q4w	100 mg q4w	Asthma	Asthma	23	Unknown	591	No	60	No
24	66F	Omalizumab	Mepolizumab	300 mg q4w	300 mg q4w	CRSwNP	HES	6	5.56	1016	No	1	No
25[f]	55 M	Omalizumab	Mepolizumab	375 mg q4w	100 mg q4w	Non-specific inflammatory lung disease	Non-specific inflammatory lung disease	13	Unknown	Unknown	No	48	No

Table 1. Characteristics of patients treated with multiple biologics simultaneously. *Abbreviations: AEC: absolute eosinophil count, IgE, immunoglobulin E; q4w, every 4 weeks; q2w, every 2 weeks; q8w, every 8 weeks; CSU, chronic spontaneous urticaria; AD, atopic dermatitis; ABPA, allergic bronchopulmonary aspergillosis; HES, hypereosinophilic syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; CRSwNP, chronic rhinosinusitis with nasal polyposis.* a. Biologic 1 was the first biologic started for every patient. b. Reference Ranges: AEC: 0.03–0.48 $\times$ 10^9/L, IgE: <214 kU/L. c. Determined by positive skin prick tests. d. Adverse events include anaphylaxis, other allergic reactions, hepatic and renal dysfunction, malignancy, pneumonia, immune dysfunction, and pregnancy-related complications. e. Patients treated with immunotherapy while on biologic therapy. f. Patient 25 was started on a 3rd biologic (dupilumab 300 mg q2w) for the same condition with no improvement. Time on 3 biologics was 24 months

benralizumab, or dupilumab.[2–7] A recent case series described 25 patients treated with a variety of biologic combinations, 15 of which were with a combination of asthma-approved biologics (IL-5+IgE, IgE + IL-4/IL-13, and IL-5+IL-4/13).[8] The duration of therapy in this series ranged from 3 to 49 months, and there were no reports of adverse effects that limited therapy.[8] In this study, we aim to identify patients treated with multiple biologics simultaneously at a large academic health system, describe the frequency of specific biologic combinations, and examine possible related safety issues with combination biologic therapies. This study was reviewed and deemed exempt by the Mayo Clinic Institutional Review Board (IRB# 22-004408).

A retrospective chart review of patients evaluated at Mayo Clinic receiving at least 2 biologics simultaneously was performed including the following key elements: demographic characteristics, indications for biologic use, baseline laboratory values, and adverse effects. Biologics evaluated included omalizumab, mepolizumab, benralizumab, and dupilumab. Patients were identified using the Epic® Slicer Dicer search tool to identify any patient with a medical record at our institution with 2 or more of the biologics of interest on their medication list simultaneously. These charts were then reviewed to determine if multiple biologics were indeed being utilized simultaneously. No patient receiving multiple biologics was excluded for any reason. The choice of biologic was determined by either the provider at the time of evaluation or an outside referring provider. The authors were not involved in the care of the patients. Specific adverse effects investigated included anaphylaxis or other allergic reactions, hepatic or renal dysfunction, malignancy, pregnancy-related complications, pneumonia while on multi-biologic therapy, and immune dysfunction.

Between January 1, 2015 and July 31, 2021, 51 patients with multiple biologics on their medication list were identified, 25 of whom were using multiple biologic medications simultaneously. The characteristics of each individual are shown in Table 1. Biologic combinations included omalizumab + mepolizumab (n = 11), omalizumab + dupilumab (n = 6), omalizumab + benralizumab (n = 4), mepolizumab + dupilumab

Characteristic	Total (n = 25)	Oma + Mepo (n = 11)	Oma + Dupi (n = 6)	Oma + Benra (n = 4)	Mepo + Dupi (n = 3)	Oma + Mepo + Dupi (n = 1)
Median age, years (min-max)	54 (12-75)	63 (12-73)	49 (26-53)	49 (27-75)	41 (40-54)	55 (55-55)
Sex, female (%)	16 (64)	7 (63.6)	4 (66.7)	4 (100)	1 (33.3)	0 (0)
Median treatment duration, months (min-max)	17.5 (1-60)	24 (1-60)	17 (1-24)	7.5 (3-12)	15 (1-24)	48 (0)
Median pre-biologic AEC[a] (min-max)	0.70 (0.20-5.56)	0.66 (0.46-5.56)	0.70 (0.20-0.95)	0.71 (0.40-1.65)	1.10 (0.40-1.40)	NA
Median pre-biologic IgE[a] (min-max)	462 (8.2-9296)	533 (14.3-1700)	462 (66.6-1958)	390 (8.2-9296)	64.3 (35.2-174)	NA
Median post-biologic AEC[a] (min-max)[b]	0.07 (0-1.17)	0.10 (0.04-0.29)	0.34 (0-1.17)	0 (0-0.09)	0.04 (0-0.20)	0
Median post-biologic IgE[a] (min-max)[b]	130.5 (19-6300)	130.5 (85-300)	617.5 (67-1168)	3404.5 (590-6300)	37.2 (19-55.3)	NA
Adverse Events[c]	0	0	0	0	0	0

Table 2. Summary of demographics, laboratory values, and outcomes. *Abbreviations: SD, standard deviation; AEC, absolute eosinophil count; IgE, immunoglobulin E; Oma, omalizumab; Mepo, mepolizumab; Dupi, dupilumab; Benra, benralizumab.* a. Reference Ranges: AEC: 0.03–0.48 $\times$ 10^9/L, IgE: <214 kU/L. b. Post-biologic refers to latest laboratory measurement while patient was still receiving multi-biologic therapy. c. Adverse events include anaphylaxis, other allergic reactions, hepatic and renal dysfunction, malignancy, pneumonia, immune dysfunction, and pregnancy-related complications.

(n = 3), and omalizumab + mepolizumab + dupilumab (n = 1). Sixteen patients were receiving multiple biologics for the same condition, the most common of which was asthma (n = 10) followed by ABPA (n = 3), CSU (n = 1), urticarial dermatitis (n = 1), and a non-specific inflammatory lung disease (n = 1). Nine patients were being treated for separate conditions, the most common combination being CSU and AD (n = 3). Other combinations included AD + hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA)+ chronic rhinosinusitis with nasal polyposis (CRSwNP), asthma + CRSwNP, asthma + EGPA, asthma + CSU, and CRSwNP + HES. A summary of demographics, laboratory values, and outcomes for each biologic combination is shown in Table 2. The median baseline absolute eosinophil count and IgE prior to initiation of any biologic was 0.70 $\times$ 10^9/L (ref 0.03–0.48 $\times$ 10^9/L) and 462 kU/L (ref <214 kU/L), respectively. The average duration of combination biologic use was 17.5 months (range 1–60 months). No patients had anaphylaxis or other allergic reactions at any point during use of multiple biologics. No new malignancies, hepatic or renal impairment, pneumonias, or immune dysfunction were reported after use of multiple biologics, and no patient became pregnant during therapy.

Our study describes one of the largest case series of combination biologic therapies assembled to date. Previous reports of 1 to 10 patients have described combining omalizumab with either an anti-TNF, anti-IL-5/IL-5R, or dupilumab for up to 2 years.[1-7] A recent series, also of 25 patients, described multiple safe and effective combinations of two different asthma-approved biologics as well as combinations of an asthma biologic with a wide range of non-asthma biologics (canakinumab, etanercept, rituximab, and ustekinumab, among others) for up to 49 months.[8] While the median duration was 17.5 months in our report (similar to previous reports), a number of patients had been maintained on dual biologic therapy for up to 60 months without significant side effects. As the indications for biologics expand, growing numbers of patients may have multiple conditions targeted with different biologics or may have one condition that could be targeted

by multiple biologics with different mechanisms of action. Our study suggests that combination biologic therapy may be safe in both instances insofar as there were no reports of anaphylaxis or other allergic reactions in our cohort. Additionally, while there was no malignancy or pneumonia reported in our cohort, a longer follow-up period is needed to more definitively determine the risk of these complications.

Weaknesses of this study include its retrospective nature, which limits the ability to draw robust conclusions regarding safety in a systematic fashion. In particular, we were unable to rigorously assess the reasoning for combining as opposed to switching biologics when more than one was used for the same condition, such as asthma. One reason documented in medical records of some (but not all) patients was the assessment that some patients had multifactorial asthma with objective evidence of both eosinophilic and allergic phenotypes such that multi-biologic therapy would be synergistic in treating both pathogenic mechanisms. The use of tezepelumab, which is known block all type 2 biomarkers by blocking TSLP upstream of the inflammatory cascade, may be an option in these patients as opposed to multi-biologic therapy. Additionally, safety of tezepelumab in trials is likely a clue to the safety of multi-biologic use in asthma given tezepelumab's aforementioned effect on multiple type 2 biomarkers.[8,9]

Additional weaknesses include the inability to perform an efficacy assessment due to limited available objective data. The retrospective design also precluded the ability to measure anti-drug antibodies or assess changes in sputum parameters. Additionally, as this study was conducted at a large academic institution, there may be referral bias that limits the generalizability of findings in our cohort to the general population. Furthermore, an important pragmatic issue involves the high costs of biologics that may limit the feasibility of combination biologic therapy. A recent study demonstrated that in patients with asthma treated with one biologic, the cost of biologics must be significantly reduced to improve cost effectiveness.[10] Therefore, in addition to factors of efficacy and safety, the costs associated with the use of multiple biologics would necessitate careful patient selection. Our study design did not afford the opportunity to perform a cost-benefit analysis, which is something that would be helpful when considering multi-biologic therapy. It should be emphasized that the use of multiple biologics is likely to be a therapeutic strategy used in a carefully selected patient population as opposed to a widespread treatment modality.

In summary, we have described 25 patients who safely tolerated combination biologic therapies targeting IgE, IL-5, IL-5R, and IL-4/IL-13. Longitudinal prospective studies are needed to determine efficacy and define the optimal patient population that may benefit from combination biologic therapy.

Abbreviations

CSU, chronic spontaneous urticaria; AD, atopic dermatitis; IL, interleukin; IL-5R, interleukin-5 receptor; ABPA, allergic bronchopulmonary aspergillosis; HES, hypereosinophilic syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; TNF, tumor necrosis factor.

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Availability of data and materials

All abstracted data is available to the readers in the tables of the manuscript.

Ethics

This study was approved by the Mayo Clinic Institutional Review Board (IRB# 22-004408).

Author contributions and consent for publication

MMP performed data collection, data analysis, and drafted the manuscript. TP is responsible for study design and critical review of the manuscript. All authors have read and consent to approval of the final manuscript.

Submission declaration

The authors declare this manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Declaration of competing interest

The authors report no conflicts of interest, financial or otherwise.

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REFERENCES

1. Fougerousse AC, Becherel PA, Pallure V, et al. Combining omalizumab with another biotherapy. *Acta Derm Venereol*. 2019;99:448–449.
2. Patel J, Ayars AG, Rampur L, Bronson S, Altman MC. Combination anti-IgE and anti-IL5 therapies in patients with severe persistent asthma and allergic bronchopulmonary aspergillosis (ABPA). *J Allergy Clin Immunol*. 2018;141:AB234.
3. Fox HM, Rotolo SM. Combination anti-IgE and anti-IL5 therapy in a pediatric patient with severe persistent asthma. *J Pediatr Pharmacol Therapeut*. 2021;26(3):306–310.
4. Thomes R, Darveaux J. Combination biologic therapy in severe asthma: a case series. *Ann Allergy Asthma Immunol*. 2018;121:S91.
5. Ortega G, Tongchinsumb P, Carr T. Combination biologic therapy for severe persistent asthma. *Ann Allergy Asthma Immunol*. 2019;123:309–311.
6. Eggert L, Chinthrajah RS. Switching and combining biologics in severe asthma: experience from a large academic teaching center. *Am J Respir Crit Care Med*. 2019;199:A1309.
7. Domingo C, Pomares X, Moron A, Sogo A. Dual monoclonal antibody therapy for a severe asthma patient. *Front Pharmacol*. 2020;11, 587621.
8. Lommatzsch M, Suhling H, Korn S, et al. Safety of combining biologics in severe asthma: asthma-related and unrelated combinations. *Allergy*. 2022:1–5.
9. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384:1800–1809.
10. Anderson WC, Szefler SJ. Cost-effectiveness and comparative effectiveness of biologic therapy for asthma: to biologic or not to biologic. *Ann Allergy Asthma Immunol*. 2019;122(4):367–372.