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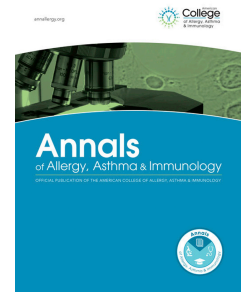
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Combination Biologic Therapy for Severe Persistent Asthma

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Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; FEV1, Forced expiratory volume in 1 second; ICS, Inhaled corticosteroid; IgE, Immunoglobulin E; IL, Interleukin; LABA, long acting beta agonist; LTRA, Leukotriene receptor antagonist. Aeroallergens: c, cat; cr, cockroach; d, dog; dm, dust mite; g, grass; m, mold; t, trees; w, weeds

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Biological pathways underlying severe asthma can be divided broadly into T2^{hi} and T2^{low}, with T2^{hi} having a greater presence of type 2 innate lymphoid and helper T cells, the cytokines interleukin (IL)-4, IL-5, IL-13 and eosinophils, while T2^{low} may show lack of inflammation or neutrophil predominance driven by Th1 and Th17 cells and the related cytokines IL-17 and interferon- γ .¹⁻³ In the past few years, more targeted biologic therapies have become available which specifically block T2 pathways and for which biomarkers such as immunoglobulin E (IgE) or blood eosinophil levels are utilized.

Omalizumab targets circulating IgE and blocks it from binding to its receptor on mast cells and basophils.⁴ Mepolizumab, reslizumab, and benralizumab target IL-5, which is key in eosinophil proliferation, activation, and recruitment.^{5,6} Dupilumab targets the IL-4 receptor alpha chain, inhibiting both IL-4 and IL-13 signaling.^{1,2} While all of these drugs have shown significant benefit for appropriate patients with severe asthma, with clinical benefit derived within days to months and all shown to reduce exacerbation frequency,⁵ modifying one pathway in the complex milieu driving asthma pathophysiology may not completely control asthma.

We have observed that some patients with severe asthma remain poorly controlled despite the use of maximal controller therapy, systemic steroids, and even after the addition of biologic monotherapy. These patients may have multiple potential therapeutic targets and the simultaneous use of multiple biologic agents could be considered. However, the use of combination biologic therapy for such patients has not been carefully studied. Here we describe our experience treating three patients with refractory disease using multiple combinations of biologic agents, for whom clinical details are summarized in Table 1.

Patient 1: A 61-year-old female with severe persistent allergic and eosinophilic asthma, allergic bronchopulmonary aspergillosis (ABPA) requiring chronic prednisone, allergic rhinitis, recurrent pneumonia and sinusitis, and severe atopic dermatitis on maximal medical therapy started treatment with omalizumab in April 2017, after which time oral steroids were successfully weaned. However, her atopic dermatitis remained severe and refractory and therefore dupilumab was added in March 2018 with marked improvement in symptoms. As of December 2018, after starting dual therapy, she has not had any exacerbations, has completely avoided oral steroids, and both the asthma and atopic dermatitis are well controlled on high dose fluticasone/salmeterol and montelukast.

Patient 2: A 60-year-old female with severe persistent eosinophilic and allergic asthma, chronic rhinosinusitis with nasal polyposis, allergic rhinitis, chronic urticaria, and chronic eosinophilic mastoiditis was receiving therapy with omalizumab for over 10 years, and while she noted some improvement in asthma symptoms on this medication, continued to require frequent courses of oral corticosteroids and high dose inhaler therapy to control her multiple diseases. As her blood eosinophil count was persistently elevated, she was started on mepolizumab in February 2016. After three months of dual biologic therapy, she successfully weaned off oral corticosteroids. In February 2018, mepolizumab was discontinued and benralizumab was started because she was still having occasional exacerbations with blood eosinophils $> 1000/\mu\text{L}$ suspected related to environmental exposures or upper respiratory infection. During the subsequent five months, she did not have any further significant asthma exacerbations. Omalizumab was therefore stopped in July 2018, however, after recurrence of allergic asthma symptoms and urticaria, was restarted in November 2018 with resolution of those symptoms.

Patient 3: A 43-year-old male with severe persistent eosinophilic and allergic asthma, ABPA, chronic rhinosinusitis, allergic conjunctivitis, and gastroesophageal reflux disease who was dependent on oral glucocorticoids despite maximal controller therapy was started on Omalizumab in May 2016. Despite the ability to wean steroids on this therapy, he continued to have frequent asthma exacerbations requiring prolonged courses of systemic steroids. Mepolizumab was added in May 2017 and this allowed him to again wean off steroids and his exacerbation rate decreased. Omalizumab was discontinued during this time, however, it was restarted in September 2017 because of worsening symptoms from presumed allergic triggers, but with minimal added benefit. He continued to have frequent exacerbations so in January 2018, mepolizumab was discontinued and benralizumab was started. He was hospitalized for asthma in October 2018 and was discharged on a prolonged steroid taper. Dupilumab was started in December 2018 and omalizumab and benralizumab were discontinued. After transitioning to dupilumab monotherapy, he has had two exacerbations but we are monitoring for signs of clinical benefit from dupilumab.

We report experience with three patients who have severe eosinophilic and allergic asthma and multiple type 2 comorbidities who were treated with simultaneous biologic therapy. These patients tolerated combination biologic therapy well and none experienced any adverse effects thought to be attributed to biologics. All of them were initially able to taper off oral glucocorticoids within a few months of starting biologic therapy. Both patients 2 and 3 saw worsening of their allergic symptoms after discontinuing omalizumab and regained some symptom control after restarting, suggesting a benefit in simultaneously targeting both the IL-5 and IgE pathways. Our experience supports considering use of dual biologic therapy, particularly for patients who remain uncontrolled on one biologic and who suffer from comorbid conditions with evidence of both allergic and eosinophilic inflammation. Allergen-

specific immunotherapy, while of potential therapeutic benefit for patients with allergic asthma, was deferred due to each patient's asthma severity and lack of control.

Safety of combination biologics for asthma has not been yet established.

Omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab all individually have favorable safety profiles with adverse event rates and infection rates similar to placebo controls, and low rates of hypersensitivity reactions.^{4,6-8} It is difficult to predict which adverse effects might be magnified by using more than one biologic but one should anticipate monitoring for infections which are primarily resolved through pathways utilizing eosinophils and mast cells.⁹ We started biologics sequentially, ensuring both necessity of the second drug and tolerability of each agent.

Cost is an important consideration, with dual biologics estimated around \$60,000 to \$80,000 per year in wholesale costs alone. This may be offset by the cost of multiple hospitalizations and lost work or school productivity. Careful patient selection is therefore necessary to maximize the potential gain from an expensive intervention.¹⁰

Patients with very severe asthma may require aggressive therapy that targets multiple relevant biologic pathways. The potential benefit of treating these patients with multiple targeted agents should be considered and studied both for efficacy, cost effectiveness, and safety.

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Patient	1	2	3
Age (years)/ Gender	61/F	60/F	43/M
Initial IgE (IU/ml)	3008	1168	9512
Initial eosinophil count (cells/uL)	200	1100	500
Eosinophil count after 6-12 months (cells/uL)	350	0	0
Severe persistent asthma	YES	YES	YES
Allergic Rhinitis or Chronic Rhinosinusitis	YES	YES	YES
ABPA	YES	NO	YES
Aeroallergen sensitivities	t/g/w/m/dm/c/d/cr	w/m/c	t/g/w/m/c
Gastroesophageal reflux disease	NO	YES	YES
Eosinophilic esophagitis	NO	NO	NO
Baseline oral corticosteroid dependence	YES	YES	YES
Smoking status	Never	Never	Former
Baseline high dose inhaled corticosteroid (ICS)	NO	YES	NO
Baseline long-acting beta agonist (LABA)	NO	NO	NO
Baseline low dose ICS/LABA	NO	NO	NO
Baseline medium or high dose ICS/LABA	YES	YES	YES
Leukotriene receptor antagonist (LTRA)	YES	YES	YES
Anti-cholinergic	YES	NO	YES
Theophylline	NO	NO	YES
Bronchial thermoplasty	NO	NO	NO
Proton pump inhibitor	NO	YES	YES
Initial FEV1	1.65 (79%)	1.65 (60%)	2.38 (61%)
FEV1 after dual therapy	Not available	2.15 (80%)	2.84 (73%)
Patient perceived improvement after 6 months	YES	YES	NO
Provider perceived improvement after 6 months	YES	YES	YES
Omalizumab start date	04/2017	1990s	05/2016
Omalizumab stop date	-	07/2018	12/2018
Omalizumab dose	150mg q4weeks	375mg q2weeks	375mg q2weeks
Mepolizumab start date	-	02/2016	05/2017
Mepolizumab stop date	-	02/2018	01/2018

Mepolizumab dose	-	100mg Qmonthly	100mg Qmonthly
Dupilumab start date	03/2018	-	12/2018
Dupilumab stop date	-	-	-
Dupilumab dose	300mg q2weeks	-	300mg q2weeks
Benralizumab start date	-	02/2018	01/2018
Benralizumab stop date	-	-	12/2018
Benralizumab dose	-	30mg q8weeks	30mg q8weeks
Hypersensitivity complications	NO	NO	NO
Infectious complications	NO	NO	NO
Autoimmune complications	NO	NO	NO
Hematologic/oncologic complications	NO	NO	NO
Exacerbations requiring hospitalization	NO	NO	Yes, hospitalized while on omalizumab/benralizumab
Able to come off oral steroids	YES	YES	YES

Table 1: Detailed patient summary of significant variables in combination biologic therapy for severe persistent asthma. FEV1 = Forced expiratory volume in 1 second; t = trees; g = grass; w = weed; m = mold; dm= dust mite; c = cat; d = dog; cr = cockroach.