

Treatment of STAT3-deficient hyper-immunoglobulin E syndrome with monoclonal antibodies targeting allergic inflammation

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Clinical Implications

Treatment with monoclonal antibodies targeting allergic inflammation in single transducer and activator of transcription 3—dominant negative (autosomal dominant hyper-immunoglobulin E syndrome) patients are well tolerated. Clinical improvements in disease severity may be seen in patients with eczematoid dermatitis, asthma, allergic bronchopulmonary asthma, and eosinophilic esophagitis.

Single transducer and activator of transcription 3 (STAT3) dominant negative (DN) is a primary immunodeficiency (PID) manifested by oto-sinopulmonary and skin bacterial infections; eczematoid dermatitis; mucocutaneous candidiasis; elevated serum immunoglobulin E (IgE); and skeletal, vascular, and connective tissue abnormalities. In recent years, monoclonal antibodies have emerged to manage atopic dermatitis (AD) and eosinophilic disease raising interest in whether STAT3 DN patients could have clinical benefit. The STAT3 DN patients express increased interleukin-4R (IL-4R)¹ and IL-5 levels² suggesting there may be utility in treatment with dupilumab, an IL-4R α antagonist,^{3,4} or benralizumab, an IL-5 receptor antagonist that has had demonstrated success in treatment of eosinophilic asthma in STAT3 DN.⁵ We summarize 17 STAT3 DN patients treated with monoclonals targeting allergic inflammation. Thirteen patients, or their guardians, provided informed consent under a National Institute of Allergy and Infectious Diseases (NIAID) institutional review board—approved natural history protocol, 3 patients at Children's Hospital of Pittsburgh provided informed consent with a standard consent form, and 1 patient was consented for the European Society for Immunodeficiencies (ESID) registry.

Seventeen patients were treated with monoclonal therapies for allergic or eosinophilic inflammation. Thirteen patients were treated with dupilumab, 1 with mepolizumab, 1 with omalizumab, and 2 with combinations or successions of monoclonals including 1 with reslizumab followed by benralizumab, and 1 with omalizumab followed in combination with mepolizumab and later omalizumab with dupilumab (Table 1).

Indications for dupilumab therapy for the 14 treated patients (including the 1 with combination therapy) included AD

(n = 7), asthma (n = 1), asthma and AD (n = 3), and acute bronchopulmonary asthma (ABPA; n = 3). Nine patients (patients 2–7 and 9–12) treated for AD reported decreased or discontinuation of topical corticosteroids and systemic antibiotics; 3 patients suffered exacerbations following treatment interruption. Patient 2 was treated with dupilumab for both asthma and AD with resolution of recurrent need for systemic corticosteroid therapy courses, reduced albuterol usage, resolution of recurrent skin infections, and significant decline in school absences (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org). For those treated for asthma, the forced expiratory volume in 1 second (FEV₁) was relatively unchanged before and after therapy for patient 8; however, all 4 patients (patients 2, 4, 8, and 12) reported less frequent rescue inhaler usage. Three patients were treated with dupilumab for ABPA. Patient 1 had azole resistant pulmonary *Aspergillus* with frequent hemoptysis, sputum production, and shortness of breath prior to initiation of dupilumab, and had both symptomatic and radiographic improvement with dupilumab treatment of 300 mg every 2 weeks (Figure 1). Of note, twice-weekly inhaled amphotericin was added, which partially may have contributed to her clinical changes, although improvement predated this addition. Patient 13 discontinued dupilumab for intolerance owing to brain fog symptoms, and patient 14 noted minimal change in symptoms and noted potential adverse effects (Table 1). Dupilumab was well tolerated by the other 12 individuals treated. The IgE levels and absolute eosinophil count (AEC) decreased while on therapy, although initial blood eosinophil count increases were seen in some patients.

Patient 17, treated with mepolizumab for asthma, reported symptom improvement with the use of a rescue inhaler prior to exercise only. Pretherapy FEV₁ was not available, but post-treatment FEV₁ was normal. Baseline AEC was greater than 10,000, but improved to 0 cells/uL post mepolizumab. Patient 14, treated with omalizumab for ABPA, had subjective improvement and decreased airway plugging on computed tomography (CT) scan, but improvement was not sustained. Baseline IgE increased from 4,547 to greater than 6,000 IU/mL, as expected. Addition of mepolizumab for clinical worsening allowed stabilization but no sustained clinical improvement. This patient later switched from mepolizumab to dupilumab with omalizumab. Both mepolizumab and omalizumab were well tolerated, but dupilumab resulted in worsening arthralgia, headache, and abdominal pain (Table 1).

Patient 16 was treated with omalizumab for ABPA with good tolerance but had poor adherence to treatment and limited follow-up to report response.

Patient 15 was treated with reslizumab for eosinophilic esophagitis (EoE) and did not have changes in IgE, but AEC decreased from 540 to 110 cells/uL with treatment. There was resolution of an eosinophilic tongue lesion. The patient was switched to benralizumab owing to insurance coverage. Episodes of dysphagia occurred approximately yearly requiring esophageal dilations despite histological remission. Reslizumab and benralizumab were well tolerated.

We describe STAT3 DN patients treated with monoclonal antibodies directed against IgE, IL-5, IL-5R, and IL-4R α .

TABLE I. Characteristics of STAT3 HIES patients and response to biologics

Clinical Information	Mutation (domain)	Biologic	Prebiologic IgE (IU/mL)	Postbiologic IgE (IU/mL) (time post therapy initiation)	Prebiologic AEC (cells/uL)	Postbiologic AEC (cells/uL) (time post therapy initiation)	Response	Adverse events
Patient 1 42-y-old female with ABPA	c.1144 C > T; p. R382W (DNA binding)	Dupilumab 300 mg every 2 wk	8,240	6,311 (1 mo) 770 (15 mo)	2,020	5,480 (1 mo) 260 (15 mo)	ABPA: improved cough, decreased frequency of thick, gray sputum, resolution of hemoptysis, improved CT chest, improved energy	None
Patient 2 15-y-old female with AD and asthma	c.1003 C > T; p.R335W (CCD)	Dupilumab 300 mg every 2 wk	4,978	1,670 (6 mo)	520	180 (6 mo) 320 (13 mo)	AD: complete resolution (initial SCORAD of 53.85 to SCORAD of 0 within 2 y) Asthma: improved with no missed school and no oral steroid courses, ACT score of 20 after 2 y, less frequent albuterol use	None
Patient 3 20-y-old male with AD	c.2137 G > T; p.V713L (transactivation)	Dupilumab 300 mg every 2 wk	41,336	12,233 (4 mo)	620	300 (7 mo)	AD: improved pruritus and appearance, rare use of topical steroids and elimination of use of topical antibiotics	None
Patient 4 18-y-old female with asthma and AD	c.1979 T > C; p.N660T (SH2)	Dupilumab 300 mg every 2 wk	1,796	2,081 (3 mo)	3,320	250 (3 mo)	Asthma: decreased chest tightness and use of rescue inhaler AD: rare use of topical steroids, flare of symptoms following pause in treatment	None
Patient 5 10-y-old female with AD	c.1110(-2) A-G (DNA binding)	Dupilumab 200 mg every 2 wk	9,918	1,265 (18 mo)	260	160 (18 mo)	AD: improved pruritus and appearance, rare use of topical steroids, improved aphthous ulcers; flare during pause of therapy	None
Patient 6 12-y-old male with AD	c.1864 A > G; p.T622A (SH2)	Dupilumab 200 mg every 2 wk	2,977	554 (12 mo)	850	480 (12 mo)	AD: improved appearance, greatly decreased use of topical steroids and topical antibiotics Resolved chalazions	None
Patient 7 22-y-old female with AD	c.1388 T > A; p.V463E (DNA binding)	Dupilumab 300 mg every 2 wk	5,842	1,703 (3 mo) 637 (15 mo)	NA	270 (3 mo) 290 (15 mo)	AD: improved appearance and pruritus, decreased use of topical steroids and topical antibiotics	None
Patient 8 27-y-old female with asthma	c.1962_1964delATC; p.I654del (SH2)	Dupilumab 300 mg every 2 wk	516	458 (4 mo)	40	70 (4 mo)	Asthma: subjectively improved with less albuterol usage and improved exercise tolerance, but still with exacerbations requiring hospitalization. PFTs unchanged	None
Patient 9 10-y-old male with AD	c.1144 C > T; p.R382W (DNA binding)	Dupilumab 200 mg every 2 wk	19,511	NA	640	NA	AD: improved appearance, prior twice-daily topical steroid use now discontinued	None
Patient 10 24-y-old female with AD	c.1861 T > G; p.F621V (SH2)	Dupilumab 300 mg every 2 wk	5,061	1,416 (5 mo)	500	690 (5 mo)	AD: improved appearance and pruritus, greatly decreased use of topical steroids	None
Patient 11 32-y-old male with AD	c.1909 G > A; p.V637M (SH2)	Dupilumab 300 mg every 2 wk	14,800	3,570 (22 mo)	600	340 (22 mo)	AD: improved appearance with temporary pause in therapy for 8 wk resulted in rapid worsening of skin lesions	None

Patient 12 15-y-old female with AD and asthma	c.1003C > T; p.R335W (CCD)	Dupilumab 300 mg every 2 wk	>2,000	9,243 (10 mo)	1,420	1,796 (10 mo)	AD: complete resolution (initial SCORAD of 80.3 to SCORAD of 0 within 20 mo), monthly abscesses with complete resolution Asthma: resolved need for oral steroid courses, no significant albuterol use, ACT score of 22 after 20 mo	None
Patient 13 34-y-old female with ABPA	c.1110(-3) C > A, (DNA binding)	Dupilumab 300 mg every 2 wk	2,557	NA	320	NA	ABPA: stopped therapy owing to AE prior to response	Brain fog
Patient 14 34-y-old female with ABPA	c.1853 G > A; p.G618D (SH2)	Omalizumab 375 mg every 2 wk (age 25)	3,920	5,367 (15 mo)	960	180 (15 mo)	ABPA: slightly improved airway plugging initially with omalizumab and then with no significant change with other additions	Dupilumab worsened arthralgias, headache, abdominal pain, skin peeling
		Omalizumab 375 mg every 2 wk/ Mepolizumab 100 mg every 4 wk (age 31)	4,547	>6,000 (4 mo)	170	80 (4 mo) 620 (1 mo)		
		Omalizumab 375 mg every 2 wk/ Dupilumab 300 mg every 2 wk (age 34)	8,000	1,200 (1 mo)	220			
Patient 15 12-y-old male with EoE	c.1909 G > A; p.V637M (SH2)	Reslizumab 70 mg every 6 wk (age 9)	>6,000	>6,000 (6 mo)	540	110 (6)	EoE: improved swallowing, decrease in choking, no recurrence of stricture, resolved eosinophilic tongue lesion Histological remission	None; lost insurance approval and switched to benralizumab
		Benralizumab 30 mg every 8 wk (age 12)	>6,000	>10,000 (11 mo)	150	0 (11 mo)		
Patient 16 21-y-old female with ABPA	c.1387_1389delGTG; p.V463del (DNA binding)	Omalizumab 375 mg every 2 wk	60,100	NA	980	NA	ABPA: nonadherent with poor follow-up	None
Patient 17 14-y-old female with asthma	c.1003C > T ; p.R335W (CCD)	Mepolizumab 100 mg every 4 wk	NA	7,860 31 mo)	>10,000	0 (0 mo) 40 (2 mo) 50 (31 mo) 100 (38 mo)	Asthma: improved on ICS/LABA, albuterol only with exercise, no steroid courses or emergency department/urgent care visits or hospitalizations	None

ACT, Asthma Control Test; AE, adverse effects; CCD, coiled-coil domain; CT, computed tomography; HIES, hyper-immunoglobulin E syndrome; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; NA, not applicable; PFTs, pulmonary function tests; SCORAD, Scoring Atopic Dermatitis; SH2, Src-like homology 2.

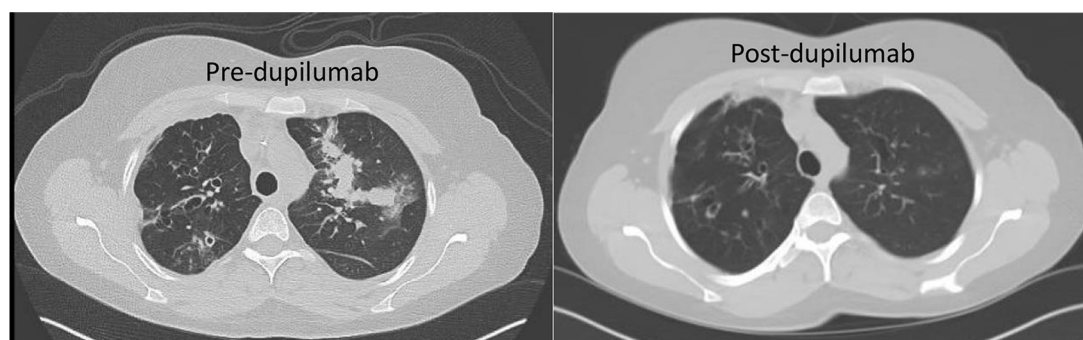


FIGURE 1. Clinical improvement for STAT3 DN patient with ABPA. Chest computed tomography scan prior to dupilumab shows bronchial wall thickening, ground-glass and tree in bud opacities, mucus plugging, nodules, and bronchiectasis. After 15 mo on treatment, improvement is visualized.

Monoclonals were overall well tolerated with 2 patients reporting adverse effects, leading to 1 stopping therapy. Conjunctivitis was not reported with dupilumab in this cohort. Dupilumab was prescribed mostly for eczematoid dermatitis, and patients reported significant improvement with decreased need for topical therapies and antibiotics. Quality of life studies were not performed, but patients reported greatly improved quality of life and formal studies are important. Also promising was the significant improvement from both an imaging and a symptom standpoint in 1 ABPA patient treated with dupilumab. Other monoclonals were prescribed less frequently but appeared well tolerated. Others have reported similar success with hyper-immunoglobulin E syndrome patients for eczema and EoE.^{4,6} Other monogenic causes of hyper-immunoglobulin E syndrome may also respond to dupilumab, and there is a report of successful treatment in a patient with ZNF341 deficiency.⁷

Future controlled clinical studies are needed to ascertain the best approaches to therapy, as well as the precise mechanism by which these biologics may be contributing to improvement in this patient population.

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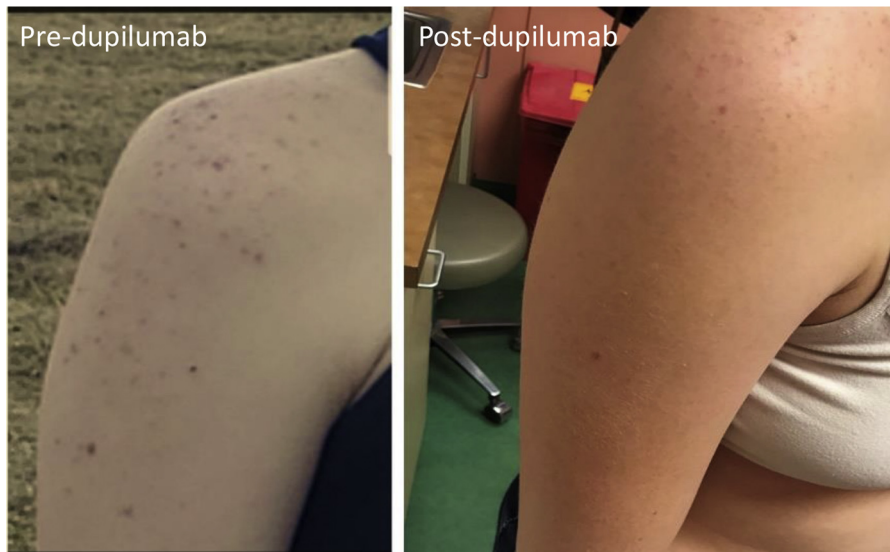


FIGURE E1. Dupilumab therapy received for eczematoid dermatitis and asthma. With dupilumab therapy, Scoring Atopic Dermatitis (SCORAD) decreased from 53.8 to 0 two years later, and she stopped requiring topical and systemic antibiotic therapies. In addition, her asthma improved and she no longer required repeated courses of systemic steroids and had reduced albuterol usage.