

breakage syndrome, Trisomy 21, Trisomy 18, ataxia telangiectasia, RAC2 dominant interfering mutation, DOCK8 deficient hyper-IgE syndrome, idiopathic T cell lymphopenia, and cartilage hair hypoplasia syndrome.

Genetic testing for *CHD7* was negative, which ruled out CHARGE syndrome. Negative testing for *TBX1* ruled out 22q11 mutation syndrome as the cause of abnormal NBS, even though our patient shared some similar features with DGA. Possibly our patient with an abnormal TRECS NBS could be considered in the spectrum of partial DGA. Mutations in *TBX1* have been reported in DGA in those without 22q11 mutation.^{5,6} Our patient initially had markedly decreased T cells, but the naïve CD4+ T cells were at a normal percentage. Over time, her T cell numbers improved, and T cell function was found to be normal. Knutsen et al had previously reported a similar pattern in a patient with DGA and abnormal NBS TRECs.⁷ The patient had decreased TRECs and decreased T cells but a normal percentage of naïve T cells. Over time, the TRECs and T cells improved.

Cytogenetic defects have been reported with decreased NBS TREC screening.⁷ To our knowledge, this is the first report of a 1q23.3q31.1 deletion in association with decreased NBS TRECs. Allergy-immunology specialists should be aware of 1q23.2q31.1 deletion in association with multiple congenital defects when evaluating abnormal TRECS on NBS in patients with similar congenital anomalies, and seeing whether the T-lymphocyte counts of those patients also normalize over time, as we observed in our patient, would be interesting.

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Mepolizumab use Post-approval academic practice experience



Severe asthma of the eosinophilic subtype is associated with significant morbidity and mortality and health-care costs due to recurrent asthma exacerbations and need for treatment with oral corticosteroids.^{1,2} Thus, steroid-sparing medications for eosinophilic asthma have been sought to improve outcomes in these patients.

Mepolizumab is a monoclonal antibody that neutralizes interleukin-5, a cytokine necessary for eosinophil hematopoiesis and eosinophilic inflammation. It has recently been approved for treatment of moderate to severe eosinophilic asthma in patients at least 12 years old. In clinical trials, mepolizumab has demonstrated significant reductions in asthma exacerbations as well as decreases in oral corticosteroid requirements when compared with placebo.^{3–6} In addition, mepolizumab has shown a beneficial effect on asthma control and quality of life, and a variable beneficial effect on lung function, when compared with placebo.^{3,4}

Mepolizumab has also been studied, with mixed results, in other eosinophilic disorders, including chronic rhinosinusitis (CRS), hypereosinophilic syndrome (HES), and eosinophilic esophagitis, but its use in treatment of these diseases is not yet approved.^{7–10}

Although clinical trials have demonstrated the efficacy and safety of mepolizumab in the treatment of asthma and other eosinophilic disorders, thus far there have been no post-approval practice-based data on its use. We examined a group of patients given mepolizumab for treatment of asthma, HES, and/or eosinophilic gastrointestinal disease (EGID) in an academic allergy-immunology clinic to evaluate its real-world effectiveness and safety.

This study was approved by the institutional review board and written informed consent was obtained from all participants. We performed a retrospective chart review of patients who had received mepolizumab 100 mg subcutaneously every 4 weeks. Data were compared 6 months before and after mepolizumab treatment. Data extracted from the medical record included demographics, relevant medical history, pulmonary function tests, blood eosinophil counts, pathology from esophagogastroduodenoscopy, and adverse outcomes related to mepolizumab. Overall efficacy of mepolizumab was assessed through global physician assessment by the treating physicians after 6 months of therapy. All statistical calculations were performed using GraphPad Prism version 7.04 (GraphPad Software, Inc, La Jolla, California). Wilcoxon matched pairs signed rank test was used for comparison of data before vs after mepolizumab treatment.

Of 58 total patients who were started on mepolizumab therapy, consent was obtained from 33 patients who had received at least

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Table 1
Baseline Characteristics and Outcomes of Interest in Patients Started on Mepolizumab for Treatment of Asthma, Hypereosinophilic Syndrome, or Eosinophilic Gastrointestinal Disease^a

	Persistent asthma (n = 28)			Hypereosinophilic syndrome (n = 4)			Eosinophilic gastrointestinal disease (n = 2)		
Clinical characteristics									
Age (mean ± SD) (years)	50.9 ± 10.0			49.5 ± 11.4			29.5		
Female sex	21 (75)			4 (100)			0 (0)		
Current or former smoker	10 (36)			2 (50)			0 (0)		
Comorbid conditions									
Persistent asthma	28 (100)			2 (50)			2 (100)		
Allergic rhinitis	23 (82)			2 (50)			1 (50)		
Chronic rhinosinusitis	23 (82)			0 (0)			0 (0)		
CRSwNP	15 (66)			0 (0)			0 (0)		
CRSsNP	4 (17)			0 (0)			0 (0)		
AERD	4 (17)			0 (0)			0 (0)		
Baseline medication use									
Daily oral corticosteroids	11 (39)			4 (100)			1 (50)		
Inhaled corticosteroid	28 (100)			1 (25)			1 (50)		
Long-acting β-agonist	24 (86)			1 (25)			1 (50)		
Omalizumab (previous use)	8 (29)								
Proton pump inhibitor				1 (25)			2 (100)		
Swallowed topical corticosteroids				0 (0)			1 (50)		
	Persistent asthma (n = 28)			Hypereosinophilic syndrome (n = 4)			Eosinophilic gastrointestinal disease (n = 2)		
Outcomes of Interest	Pre	Post	P	Pre	Post	P	Pre	Post	P
Eosinophil count (absolute number/mm ³)	1,458 ± 1,503	105 ± 103	<.0001	3,375 ± 2,056	75 ± 50	.13	4,650	200	
FEV ₁ pre-bronchodilation (liters) (mean ± SD)	1.8 ± 0.9	1.9 ± 1.0	.046						
Daily prednisone dose (mg) (mean ± SD)	9.6 ± 3.6	4.7 ± 4.6	.02	13.8 ± 4.8	3.5 ± 2.4	.13			
Oral steroid courses in 6 months (mean ± SD)	2.2 ± 1.7	0.9 ± 1.2	<.0001	1.5 ± 0.6	0.3 ± 0.5	.13			
Asthma exacerbations in 6 months (mean ± SD)	2.1 ± 1.7	0.9 ± 1.4	<.0001						
Improvement in control of disease [n (%)]		26 (93)			4 (100)			2 (100)	

Abbreviations: AERD, aspirin-exacerbated respiratory disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyps; FEV₁, forced expiratory volume in 1 second.

^aData expressed as number (%) unless noted otherwise.

6 months of continuous treatment with mepolizumab. Indications for mepolizumab included asthma (28 patients), HES (4 patients), and EGID (1 patient). One patient from the asthma group had comorbid EGID and was also used in the EGID analysis. Baseline characteristics for all groups are shown in Table 1.

In patients with asthma, blood eosinophil counts, number of asthma exacerbations, and oral corticosteroid courses decreased significantly with mepolizumab treatment (Table 1). There was a small but significant improvement in forced expiratory volume in 1 second after treatment (1.8 ± 0.9 vs 1.9 ± 1.0 L; *P* = .0459). The 11 patients who began mepolizumab while on maintenance daily prednisone were able to significantly reduce their daily dose (Table 1). Based on overall global physician assessment after 6 months of treatment, 26 patients (93%) had improvement in asthma control. We also assessed comorbid CRS control in 20 patients, and 10 (50%) showed improvement by global physician assessment after 6 months of mepolizumab.

All 4 patients with HES had skin involvement, 1 with cardiac involvement and 1 with gastrointestinal involvement. All *P* values were nonsignificant given the small sample size. Blood eosinophil counts, number of corticosteroid courses, and daily corticosteroid doses all decreased with treatment (Table 1). One patient was able to discontinue maintenance prednisone. On global physician assessment, all patients had improved control of their disease while on mepolizumab.

The 2 patients with EGID had both eosinophilic esophagitis and eosinophilic gastroenteritis. Peripheral blood eosinophils decreased with mepolizumab treatment (Table 1). The first patient

had a decrease in eosinophils per high-power field on biopsy after 2.5 months of treatment (esophagus, 100 vs 15; stomach, 60 vs 0). His prednisone dose was decreased from 10 to 2.5 mg/d while on mepolizumab. The second patient had an increase in eosinophils per high-power field on biopsy after 16 months of treatment (esophagus, 19 vs 25; stomach, 20 vs 45). He was weaned off oral budesonide 6 months after starting mepolizumab. On global assessment by physician, both patients showed overall improvement.

There were few adverse effects associated with mepolizumab. A 36-year-old male developed shingles, which resolved with valacyclovir treatment. A 55-year-old female developed trigeminal neuralgia, which improved quickly and was thought unrelated to mepolizumab. Four patients complained of new-onset fatigue. Despite these adverse effects, all patients were able to continue with mepolizumab treatment.

In this study we have presented data on the real-world effectiveness of mepolizumab for patients with eosinophilic asthma and other eosinophilic disorders. In accordance with previous clinical trials, mepolizumab treatment resulted in a significant reduction in the number of asthma exacerbations and in oral corticosteroid use.^{3–5} There was a small but significant improvement in lung function as measured by forced expiratory volume in 1 second. On physician's global assessment of asthma control, almost all patients improved. There was a high prevalence of comorbid CRS in our asthmatic patient population and approximately half showed improved CRS control with mepolizumab, based on global physician assessment. In patients with HES and EGID, there was a trend toward decreased use of oral corticoste-

roids in both groups and improvement in global assessment of disease control.

Overall, mepolizumab seems to be safe, although we acknowledge that our study was small and only a limited time frame of treatment was assessed. The most common adverse effect reported was fatigue, which may be explained by decreased corticosteroid dose and underlying mild adrenal insufficiency.

Our study has several limitations. The data were retrospective and there was no control group. The results may be biased given patients who remained on mepolizumab for more than 6 months were those who tended to have benefit. In addition, we used global physician assessment rather than a validated questionnaire to measure disease control. Nevertheless, the findings reflect real-life clinical practice in an ambulatory clinic.

In conclusion, real-world treatment with mepolizumab is effective for eosinophilic asthma and other eosinophilic disorders, with minimal adverse effects.

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Mast cell disorders

Protean manifestations and treatment responses



Mast cell disorders represent an emerging disease category notable for the diverse spectrum of presentations. Patients are clinically characterized by symptoms reflective of mast cell mediator release, which often includes episodes of urticaria with or without angioedema and flushing, as well as episodes of recurrent potentially life-threatening anaphylaxis. Multiple systems can be targeted including cardiovascular, gastrointestinal (GI), psychiatric, respiratory, and musculoskeletal. In addition, patients may have vague, nonspecific complaints, such as abdominal discomfort or “brain fog.” Triggers are often unknown and episodes follow an unpredictable pattern. The diagnosis can be elusive due to the variable clinical history and laboratory values that fluctuate depending on time of collection in relationship to a symptomatic episode.

To heighten awareness of this disease and inform clinicians on therapeutic options, we describe a cohort of 7 patients with systemic mast cell disorders. For a diagnosis of mast cell activation syndrome (MCAS),¹ patients require all 3 of the following diagnostic criteria: (1) intermittent symptoms of mast cell activation involving at least 2 organ systems; (2) improvement with pharmacologic therapy targeting mast cell mediators; and (3) laboratory evidence of increased mast cell mediators (commercially available and validated markers of mast cell activation include serum tryptase, urinary *N*-methylhistamine, prostaglandin D₂ and its metabolite 11- β -prostaglandin F₂, and leukotriene E₄). Systemic mastocytosis (SM)² patients require 1 major criterion (atypical mast cell clusters in bone marrow) and 1 minor criterion, or at least 3 minor criteria: (1) tryptase >20 ng/mL; (2) atypical mast cell

morphology; (3) aberrant expression of C2 and CD25 on mast cells; or (4) presence of the D816V c-Kit mutation. Based on these criteria, patients 1 through 5 were categorized with MCAS and patients 6 and 7 were diagnosed with indolent SM (Table 1).

Patients 1, 2, and 4 had markedly different presumed secondary activation profiles. All had evidence of either immunoglobulin E (IgE) or non-IgE secondary MCAS but also exhibited abnormal serum and/or urinary markers. The presence of secondary triggers does not always equate to secondary mast cell activation. Both systemic venom responses and hypotensive anaphylaxis, for example, may be due to an underlying primary mast cell disorder. Patient 1 presented with recurrent anaphylaxis from various foods, including 1 episode in which intubation was narrowly avoided. Of concern in this case were the recurrent severe anaphylaxis episodes and persistently abnormal baseline tryptase elevations. As such, patient 1 may warrant close surveillance despite his presumed secondary MCAS classification for evolving SM. Patient 2 exhibited mast cell activation due to an opioid medication. Emerging evidence has described non-IgE-mediated mast cell activation of opioids involving the MRGPRX2 receptor.² Patient 3 manifested cutaneous, respiratory, and GI symptoms with elevated tryptase and urinary markers. Patient 4 was diagnosed with Kounis syndrome in which ST-elevation myocardial infarction immediately followed pork consumption. Pork-specific IgE was positive and galactose- α -1,3-galactose IgE testing was negative. Kounis syndrome is a rare disorder characterized by an acute coronary syndrome triggered by the release of inflammatory mediators following an allergic insult, and has been described with underlying MCAS.³ Patient 5, with recurrent idiopathic anaphylaxis (IA), had a normal baseline tryptase with meaningful (>20% above baseline tryptase plus 2 ng/mL) symptomatic elevation along with increased urinary markers, thus meeting criteria for the IA subset of MCAS.¹

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