

Clinical Communications

Successful treatment of idiopathic hypereosinophilic syndrome with benralizumab in a pediatric patient

Maria A. Forero Molina, MD, Kara E. Coffey, MD, and Hey J. Chong, MD, PhD

Clinical Implications

- This is the first case of a pediatric patient with idiopathic hypereosinophilic syndrome (I-HES) associated with significant end-organ damage including heart failure and arrhythmia successfully treated with benralizumab, providing an additional therapeutic option for I-HES in the pediatric population.

Hypereosinophilic syndrome (HES) is a heterogeneous group of disorders characterized by the presence of marked peripheral hypereosinophilia (absolute eosinophil count [AEC] $\geq 1.5 \times 10^9/\text{L}$) with associated end-organ damage.¹ HES is classified into several clinical subtypes according to etiology and therapeutic responses. Patients in whom the underlying etiology is unknown are classified as idiopathic HES² (I-HES). Reducing blood and tissue eosinophilia is the major treatment goal as end-organ damage related to eosinophils can lead to significant morbidity and mortality.³ First-line therapy includes corticosteroids, although chronic use leads to significant side effects, and not all patients are steroid-responsive.^{4,5} Monoclonal antibodies against IL-5 activity have the ability to deplete eosinophils rapidly and specifically, representing a promising alternative therapy.²⁻⁵ HES is more commonly diagnosed in adults; however, there have been reports in children.^{1,5-7} Treatment in children is challenging given the relative paucity of literature on the subject. Mepolizumab (monoclonal antibody) has been successfully used in pediatric HES.⁵⁻⁷ Recently, benralizumab (an IL-5 receptor- α [IL-5R α] antagonist) showed clinical benefit compared with placebo in adults with PDGFRA-negative HES.⁸ We present the case of a child with I-HES who responded to benralizumab. To our knowledge, this is the first report of successful use of benralizumab in a pediatric patient with HES.

A 9-year-old girl presented to the emergency department with a 2-month history of weight loss, fatigue, rash, and diarrhea. In the preceding 2 years, she was treated for severe eczema with methotrexate and cyclosporine, with documented chronic peripheral hypereosinophilia lasting longer than 6 months with the peak AEC of $4.43 \times 10^9/\text{L}$. Skin findings were notable for diffuse lichenification and hypopigmentation. Initial laboratory findings included a white blood cell count of $19.4 \times 10^9/\text{L}$ (AEC $1.75 \times 10^9/\text{L}$ on presentation that peaked at $3.3 \times 10^9/\text{L}$), normocytic anemia with hemoglobin of 7.7 g/dL, and elevated inflammatory markers. Hypokalemia, hyperchloremia, and hypoalbuminemia were noted with total serum albumin <1.0 g/dL. Diagnostic studies were performed to exclude infectious, malignant, or immunodeficiency etiologies, including a bone marrow biopsy notable for relative hypereosinophilia (10% of cells without

evidence of neoplasm), endoscopies with normal pathology, and skin biopsy consistent with atopic dermatitis. On hospital day 3, she developed a new cardiac murmur, and an echocardiogram showed mild left ventricle dilation with mildly depressed function (left ventricular ejection fraction [LVEF] = 43%). Given cardiac, bone marrow, and skin involvement, she was treated for HES with high-dose corticosteroids pending additional immune and genetic workup. On hospital day 13, she started a 3-day pulse of methylprednisolone IV 10 mg/kg/day but had already developed a large right-sided pleural effusion requiring chest tube placement; the pleural fluid contained 33% eosinophils. Cardiac magnetic resonance imaging demonstrated severely depressed right- and left-ventricular function (LVEF = 25%), and she was transferred to the intensive care unit given worsening respiratory distress and cardiac dysfunction. She required milrinone for heart failure and anticoagulation for a right atrial thrombus. The AEC rapidly plummeted from $1.7 \times 10^9/\text{L}$ to zero 4 days after steroid initiation, and milrinone was weaned off after 1 week with resolution of cardiac dysfunction.

After dramatic reversal of her heart failure, corticosteroids were slowly tapered, with the resultant rise in the AEC ($0.28 \times 10^9/\text{L}$ at hospital discharge). Additional studies showed negative fluorescence in situ hybridization for *FIP1L1-PDGFR α* , *ETV6*, and *BCR/ABL1*. T-cell receptor gene rearrangement studies and TCR Vbeta repertoire studies sent to Cincinnati Children's diagnostic immunology laboratory were normal. Whole-exome gene sequencing done through Centogene did not reveal any pathologic or variants of unknown significance. Three months after discharge, with mepolizumab denied by insurance, she was started on imatinib as a steroid-sparing agent in addition to prednisone 20 mg/day, given the literature that supports the use of imatinib in *FIP1L1-PDGFR α* -negative patients.²

Four months after imatinib initiation, she presented with septic shock and acute renal failure (blood culture positive for methicillin-susceptible *Staphylococcus aureus*, creatinine of 16.5 mg/dL). On admission, the AEC was $0.05 \times 10^9/\text{L}$. She required vasopressors, antibiotics, stress-dosed hydrocortisone (HCT), and dialysis. She developed acute respiratory failure requiring intubation and mechanical ventilation. HCT was weaned off on hospital day 9 as her clinical picture stabilized and the AEC rebounded quickly thereafter, peaking at $4.47 \times 10^9/\text{L}$ on hospital day 20, at which point intravenous methylprednisolone 4 mg/kg/day was started (Figure 1, A). An echocardiogram showed a decline in left ventricular systolic function, and she developed torsades de pointes with 2 episodes of pulseless ventricular tachycardia requiring cardiopulmonary resuscitation and defibrillation on hospital day 22. In the setting of ongoing peripheral eosinophilia with life-threatening cardiac dysfunction, we received innovative consent to try benralizumab 30 mg subcutaneously to treat refractory hypereosinophilia (Figure 1, B), which was well tolerated. Respiratory, cardiac, and nutritional supports were weaned and methylprednisolone was slowly tapered, after which she began physiologic HCT replacement therapy. Her profound cardiac and renal complications resolved by hospital discharge on day 64. Dedicator of cytokinesis 8 functional test done through Seattle Children's diagnostic immunology laboratory was normal. She continues on

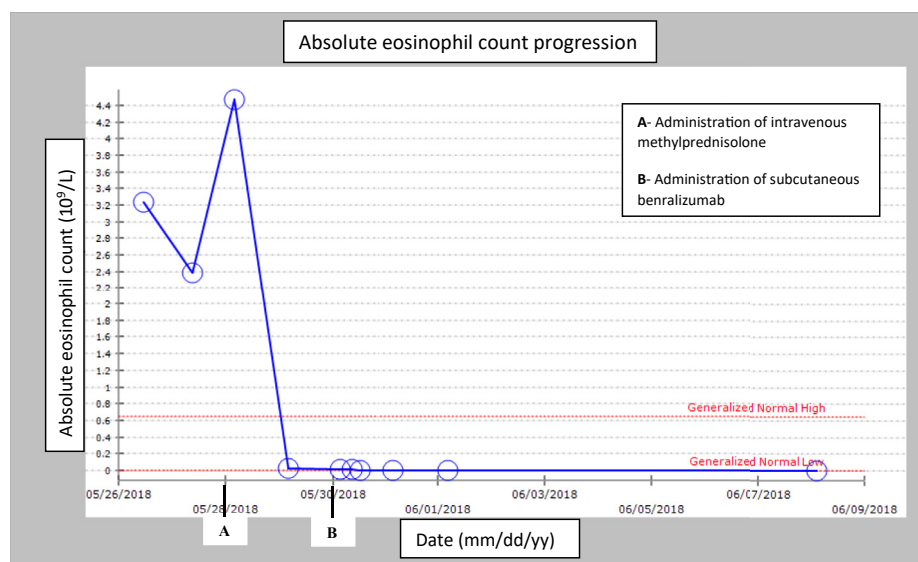


FIGURE 1. Absolute eosinophil count before and after initiation of (A) intravenous methylprednisolone and (B) subcutaneous benralizumab.

benralizumab, now dosed every other month. Eosinophil count remains under $0.3 \times 10^9/L$ 18 months after initiation of benralizumab therapy without steroids. Her severe skin findings also showed significant improvement on this medication.

I-HES in children is rare, and although corticosteroids remain first-line treatment, the anti-IL-5 monoclonal antibody mepolizumab has been successfully used in pediatric patients for this condition.⁵⁻⁷ In our case, attempts for insurance approval for off-label use of mepolizumab were denied. Given her critical illness, we received innovative consent to use benralizumab. This medication is used for eosinophilic asthma in patients older than 12 years and is overall well tolerated with its described safety profile.^{8,9} Given the heterogeneity of HES, additional therapeutic targets such as the IL-5R α chain can be beneficial, as demonstrated in this case. Although recent clinical trial evidence supports benralizumab in adults with HES, more evidence is needed in pediatric patients.⁸ To our knowledge, this is the first report of the successful use of an IL-5R α antagonist in a pediatric patient with I-HES, though further studies are necessary to demonstrate its long-term efficacy in pediatric HES.

Division of Allergy and Immunology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pa

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 22, 2020; revised August 12, 2020; accepted for publication August 13, 2020.

Available online ■ ■

Corresponding author: Hey J. Chong, MD, PhD, Division of Allergy and Immunology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224. E-mail: hey.chong@chp.edu.

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.08.034>

REFERENCES

- Burris D, Rosenberg CE, Schwartz JT, Zhang Y, Eby MD, Abonia JP, et al. Pediatric hypereosinophilia: characteristics, clinical manifestations, and diagnoses. *J Allergy Clin Immunol Pract* 2019;7:2750-2758.e2.
- Klion AD. How I treat hypereosinophilic syndromes. *Blood* 2015;126:1069-77.
- Kuang FL, Klion AD. Biologic agents for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol Pract* 2017;5:1502-9.
- Dispenza MC, Bochner BS. Diagnosis and novel approaches to the treatment of hypereosinophilic syndromes. *Curr Hematol Malig Rep* 2018;13:191-201.
- Schwarz C, Müller T, Lau S, Parasher K, Staab D, Wahn U. Mepolizumab—a novel option for the treatment of hypereosinophilic syndrome in childhood. *Pediatr Allergy Immunol* 2018;29:28-33.
- van Grotel M, de Hoog M, de Krijger RR, Beverloo HB, van den Heuvel-Eibrink MM. Hypereosinophilic syndrome in children. *Leuk Res* 2012;36:1249-54.
- Williams KW, Ware J, Abiodun A, Holland-Thomas NC, Khoury P, Klion AD. Hypereosinophilia in children and adults: a retrospective comparison. *J Allergy Clin Immunol Pract* 2016;4:941-947.e1.
- Kuang FL, Legrand F, Makiya M, Ware J, Wetzler L, Brown T, et al. Benralizumab for PDGFRA—negative hypereosinophilic syndrome. *N Engl J Med* 2019;380:1336-46.
- Jackson DJ, Korn S, Mathur SK, Barker P, Meka VG, Martin UJ, et al. Safety of eosinophil-depleting therapy for severe, eosinophilic asthma: focus on benralizumab. *Drug Saf* 2020;43:409-25.