

Two pediatric cases of ANCA-negative eosinophilic granulomatosis with polyangiitis successfully treated with dupilumab



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Clinical Implications

- The first report of successful treatment of antineutrophil cytoplasmic antibody-negative eosinophilic granulomatosis with polyangiitis in 2 patients using dupilumab after progression of disease on mepolizumab. Short-term overlap of mepolizumab with dupilumab may address the transient eosinophilia that can be seen with dupilumab.

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) is a chronic heterogeneous disease characterized by asthma, rhinosinusitis, and eosinophilic vasculitis. Patients with refractory disease are often dependent on systemic glucocorticoids or other immunosuppressants. In 2017, mepolizumab, an anti-IL-5 monoclonal antibody (mAb), shown to reduce severe exacerbations in eosinophilic asthma,¹ was FDA-approved for adults with EGPA. However, approximately 47% of patients on mepolizumab did not reach protocol-defined remission.²

Dupilumab is a fully human mAb directed against the alpha subunit of the IL-4 receptor, blocking both IL-4 and IL-13 signaling, critical mediators of T2 inflammation. Dupilumab is approved for moderate-to-severe eosinophilic asthma, moderate-to-severe atopic dermatitis, and chronic rhinosinusitis with nasal polyposis (CRSwNP). In eosinophilic asthma, dupilumab can reduce severe asthma exacerbations and systemic glucocorticoid requirements.^{3,4} In CRSwNP, dupilumab can reduce polyp size and severity of symptoms.⁵ We therefore postulated that dupilumab could be used in patients with EGPA with incomplete improvement on mepolizumab.

In case 1, a 13-year-old boy was diagnosed with asthma and allergic rhinitis after 2 years of episodic shortness of breath and chronic nasal congestion. He had had 4 to 5 hospitalizations per year for acute asthma exacerbations and sinusitis. Omalizumab and allergen immunotherapy were initiated, but symptoms progressed.

Laboratory studies revealed prominent peripheral eosinophilia (1600 cells/ μ L) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Computed tomography (CT) chest showed bilateral peripheral patchy consolidations (Figure 1, A). Bronchoalveolar lavage (BAL) demonstrated a mixed infiltrate with 19% eosinophils (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). He was

diagnosed with CRSwNP and underwent endoscopic sinus surgery (ESS) with biopsy revealing eosinophilic and granulomatous inflammation (Figure 1, B). Antineutrophil cytoplasmic antibodies (ANCA) were negative. Spirometry revealed a forced expiratory volume in 1 second (FEV1) of 35% predicted, and fractional exhaled nitric oxide (FeNO) was 75 parts per billion (ppb).

He was initially treated with budesonide/formoterol fumarate dihydrate 160 mcg/4.5 mcg 2 puffs twice daily, montelukast daily, albuterol as needed, and prednisone 2 mg/kg/day. The patient's symptoms improved; however, he developed significant flares on tapering of corticosteroid. He was switched to mometasone furoate/formoterol fumarate dihydrate 200mcg/5 mcg 2 puffs twice daily, however, he was unable to reduce his corticosteroid dose from 15 mg prednisone daily. He was started on mepolizumab 100 mg monthly; however, in light of his sinus disease, granulomatous inflammation, pulmonary infiltrates, and severe airway disease, he was diagnosed with ANCA-negative EGPA. Therefore, mepolizumab was increased to 300 mg monthly. Although his lung function and eosinophilia improved (Table E1, available in this article's Online Repository at www.jaci-inpractice.org; Figure 2), he had frequent asthma exacerbations consisting of 4 emergency department (ED) visits and 1 hospitalization over the course of 1 year, the latter complicated by sinusitis with preseptal cellulitis. He received a trial of rituximab, as recommended by rheumatology; however, despite repeat ESS and twice daily budesonide sinus rinses, nasal symptoms progressed. He subsequently developed corticosteroid-associated complications including bone density loss and adrenal insufficiency. Three months after stopping rituximab, dupilumab was initiated in light of his severe sinus disease and asthma refractory to mepolizumab.

While continuing mepolizumab 300 mg monthly, he received a 600 mg loading dose of dupilumab followed by 300 mg every 14 days. To reduce the injection burden, mepolizumab was stopped after 1 month overlap with dupilumab. In the 10 months since starting dupilumab, he has had no asthma exacerbations requiring ED visits or hospitalizations. Asthma Therapy Assessment Questionnaire scores, which had decreased to 2 on mepolizumab, were consistently 0 on dupilumab. FeNO decreased from 75 ppb on mepolizumab monotherapy to 11 ppb on dupilumab monotherapy, indicating reduced T2 inflammation (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). FEV1 increased from 54% on mepolizumab alone to 102% on mepolizumab/dupilumab combination therapy and remained within the normal range when mepolizumab was discontinued (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Patient-reported nasal symptoms improved, and endoscopic examinations failed to show return of polyps. Eosinophil count mildly increased from 0 cells/ μ L on mepolizumab monotherapy to 200 cells/ μ L on dupilumab monotherapy (Figure 2). After transitioning to dupilumab monotherapy, corticosteroids were weaned slowly over the course of 4 months due to concern for hypothalamic-pituitary axis compromise. In the 5 months since completing the steroid taper, no additional oral steroids have been prescribed.

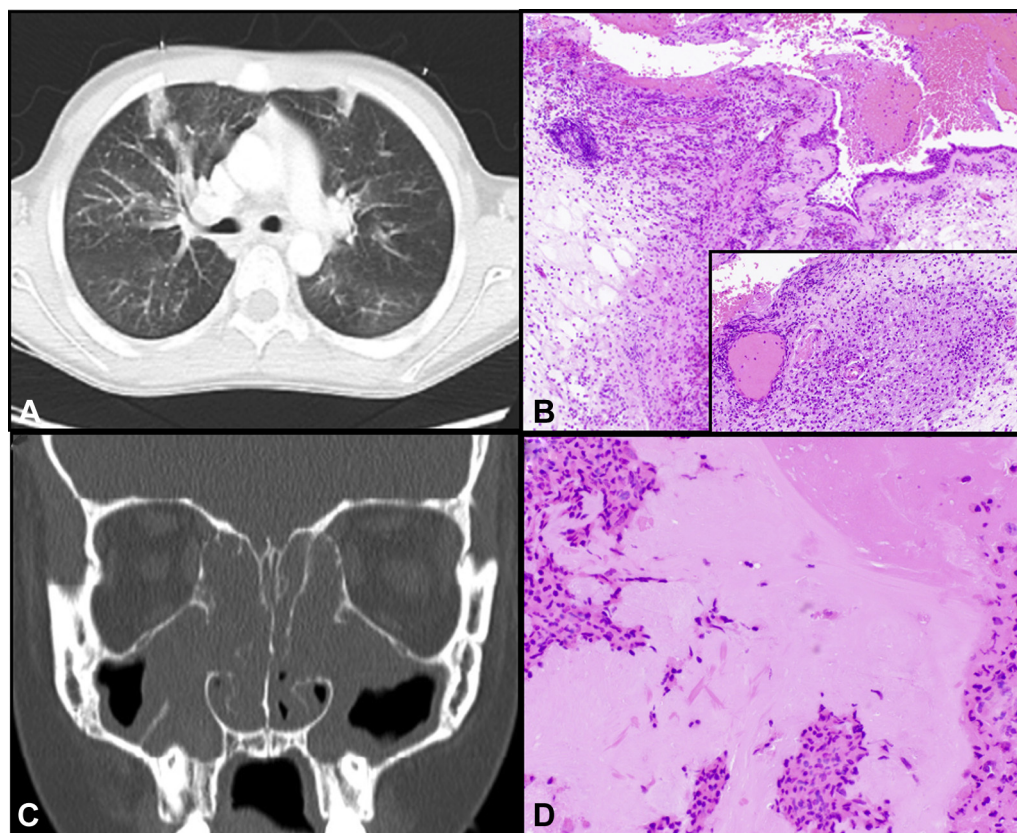


FIGURE 1. Representative images of 2 children with ANCA-negative EGPA. **A**, Computed tomography (CT) scan of the thorax demonstrating patchy airspace consolidation with upper lobe ground-glass opacities. **B**, H&E stain of nasal polyp biopsy showing inflammatory polyp with abundant eosinophils and edema. Noncaseating granulomas highlighted in the high-power inset. **C**, Maxillofacial CT demonstrating severe bilateral pansinusitis. **D**, H&E stain from nasal polyp biopsy showing degenerating eosinophils with Charcot-Leyden crystals. *ANCA*, Antineutrophil cytoplasmic antibodies; *EGPA*, eosinophilic granulomatosis with polyangiitis; *H&E*, hematoxylin and eosin.

In case 2, a 16-year-old girl presented at age 9 with facial eczematous rash and chronic nasal congestion. Two years later, she developed chronic cough and wheezing with weekly ED visits despite an aggressive controller regimen. CT chest showed central bronchiectasis and hilar adenopathy. Laboratory studies revealed peripheral eosinophilia (10,100 cells/ μ L) and BAL demonstrated 28% eosinophils. Initial FEV1 was 45% predicted (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Concurrently, she was diagnosed with CRSwNP. She was started on prednisone up to 25 mg daily but experienced significant flares on tapering. She underwent ESS at age 13, which improved symptoms transiently, but polyps recurred. In light of her CT imaging findings, severe eosinophilic asthma, and severe sinus disease, she was diagnosed with ANCA-negative EGPA.

She was started on a trial of rituximab by rheumatology; however, her pansinus disease persisted (Figure 1, C). Biopsy from her second ESS demonstrated significant eosinophilic infiltrates without vasculitis or granuloma (Figure 1, D). Her asthma was well controlled on mometasone furoate/formoterol fumarate dihydrate 200 mcg/5 mcg 2 puffs twice daily and albuterol as needed. Months later, her sinus disease worsened despite 10 mg prednisone daily and twice daily budesonide sinus rinses.

Mepolizumab was started at 300 mg monthly. Two months later, although her eosinophil count significantly decreased, her sinus symptoms remained severe requiring a third ESS. In light of her severe sinus disease, dupilumab was then initiated with a 600 mg loading dose and then 300 mg every 14 days. Within 2 months, her sinus disease improved. She did not have any asthma exacerbations requiring ED visits or hospitalizations before or after starting dupilumab therapy. In addition, her skin disease significantly improved. Mepolizumab was stopped after a 2-month overlap with dupilumab. Her last course of prednisone was 1 month before initiating dupilumab, and over the 7 months of follow-up on dupilumab monotherapy, no additional courses of corticosteroids were prescribed. Nasal endoscopic examinations have failed to demonstrate return of polyps, and, importantly, her eosinophil count has remained low after transition to dupilumab monotherapy (Figure 2).

We present, to our knowledge, the first cases of dupilumab efficacy in mepolizumab-refractory ANCA-negative EGPA in children. There is a clinical need to find additional targeted therapies for EGPA. Widespread inactivation of the T2 pathway with dupilumab, by blocking IL-4-mediated IgE class switching as well as IL-13-induced airway remodeling, may be beneficial in

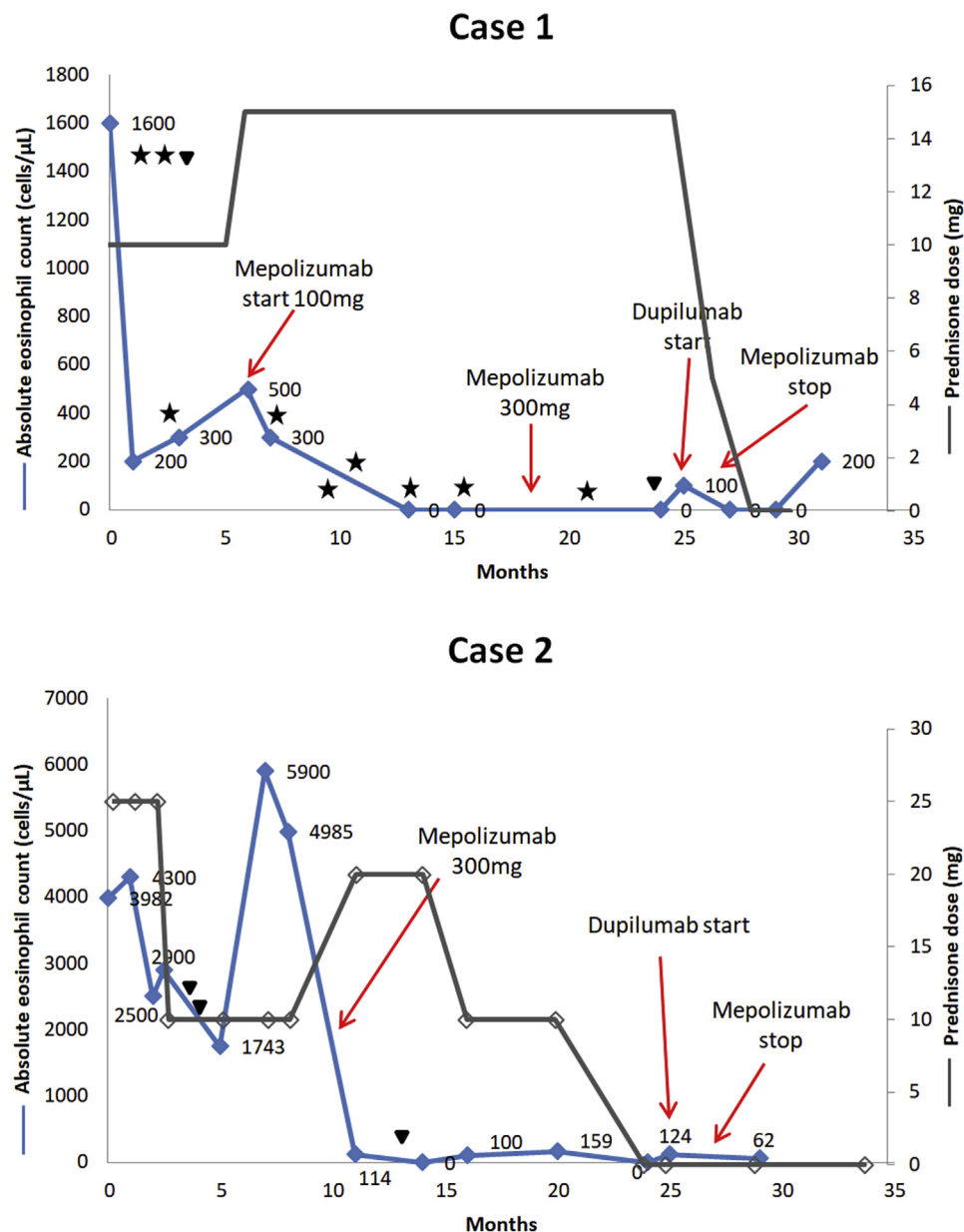


FIGURE 2. Graphical representation of the clinical course of 2 children with ANCA-negative EGPA. Absolute eosinophil counts are reported in the left Y-axis (trend shown in blue), the right Y-axis corresponds to the doses of prednisone prescribed during the follow-up interval (trend shown in gray), and the X-axis denotes months of treatment. Of note, corticosteroids were taken continuously in case 1, whereas in case 2, corticosteroids were taken in multiple tapered doses; therefore, the dosages listed for case 2 are estimates based on prescribing information as precise doses corresponding to the dates of lab draws are difficult to discern. Stars in case 1 denote asthma exacerbations requiring an ED visit or hospitalization. Downward triangles represent the dates of sinus surgery. ANCA, Antineutrophil cytoplasmic antibodies; ED, emergency department; EGPA, eosinophilic granulomatosis with polyangiitis.

some patients with EGPA. Particularly in children, reducing the cumulative corticosteroid exposure is particularly important.

EGPA is a heterogeneous disease, and therefore other differential diagnoses require consideration. Chronic eosinophilic pneumonia (CEP) was an initial diagnostic consideration in case 1; however, the patient developed sinus disease and nasal polypsis later in his clinical course. In case 2, a diagnosis of allergic bronchopulmonary aspergillosis (ABPA) was considered;

however, high-grade eosinophilia is unusual in ABPA and specific IgE to *Aspergillus fumigatus* was negative. Also, although sinus culture from her first ESS did grow scant *A. fumigatus*, this was thought to be due to colonization in the setting of frequent antibiotic use as her clinical course did not suggest invasive aspergillosis. It is important to note that both patients demonstrated more of an atopic rather than vasculitic phenotype, without pericardial, renal, or neurologic disease. However, aside from age,

both patients met inclusion criteria for the 2017 mepolizumab for EGPA randomized controlled trial with asthma plus eosinophilia, pulmonary infiltrates, and sinonasal disease.² Of note, we are unable to determine whether dupilumab would have improved disease outside of the sinuses or lungs. It has been previously reported that chronic corticosteroid use can suppress manifestations of the disease, initially described as “forme fruste” and can also alter absolute eosinophil counts potentially obscuring the diagnosis.⁶ Therefore, it is unclear whether the patients would have gone on to develop additional manifestations of EGPA in the absence of therapy.

Both patients were ANCA-negative; therefore, we are unable to state how dupilumab would perform in ANCA-positive patients. However, data supporting a distinct ANCA-associated phenotype are lacking, and as such, clinical manifestations typically guide therapy independent of ANCA status.⁷ Future investigations can identify subgroups of patients with EGPA who may benefit from combined mepolizumab/dupilumab, transitional overlap, or dupilumab monotherapy. For example, EGPA manifestations have been found to differ in children compared with adults. In the French Vasculitis Study group cohort, children were found to have increased ENT symptoms and biopsies showing fewer features of vasculitis.⁸ Dupilumab efficacy may as well differ in children compared with adults. Importantly, dupilumab is likely to be more effective in EGPA patients with prominent sinus disease compared with mepolizumab monotherapy.⁹ Additional data are also needed to clarify the optimal dose and duration of dupilumab treatment.

These 2 cases address concerns regarding transient eosinophilia seen in up to 14% of patients treated with dupilumab in clinical trials. The majority of transient eosinophilia was asymptomatic and most eosinophil levels returned to normal.⁴ Although dupilumab blocks migration of eosinophils into tissues, it does not prevent egress of eosinophils from the bone marrow, which is influenced by IL-5. In the paper by Castro et al,³ there were, however, 4 serious cases of peripheral eosinophilia (>3000 cells/ μ L) with 1 worsening case of CEP. The absence of a significant increase in eosinophils after initiation of dupilumab in our cases could be due, in part, to overlap with mepolizumab. Further investigation can elucidate if such an overlap could be considered in patients with high baseline eosinophil burden.

This case series suggests that dupilumab may be effective in mepolizumab-refractory ANCA-negative EGPA. These results open the door for further clinical uses and studies of dupilumab in this patient population.

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ONLINE REPOSITORY

TABLE E1. Case summaries

Characteristic	Case 1	Case 2
Age	14	16
Sex	Male	Female
ANCA status	Negative	Negative
Tried therapies	Omalizumab Rituximab Mepolizumab	Methotrexate Adalimumab Rituximab Mepolizumab
No. of sinus surgeries	2	3
Bronchoalveolar lavage cellular differential	39% neutrophils 9% lymphocytes 30% macrophages 19% eosinophils	28% eosinophils NA NA NA
FEV1 (% predicted/post bronchodilator change)		
Before mepolizumab	34/18	45/NA
Mepolizumab alone	54/10	112/NA
Mepolizumab and dupilumab	102/17	119/NA
Dupilumab alone	84/8	116/NA
Total IgE (IU/mL)		
Before mepolizumab	408	1058/155*
Mepolizumab alone	366	92
Mepolizumab and dupilumab	191	NA
Dupilumab alone	NA	NA
FeNO (ppb)		
Before mepolizumab	NA	24
Mepolizumab alone	75	NA
Mepolizumab and dupilumab	18	NA
Dupilumab alone	11	NA
ATAQ [†] score		
Before mepolizumab	6	3
Mepolizumab alone	2	0
Mepolizumab and dupilumab	0	1
Dupilumab alone	0	0

ANCA, Antineutrophil cytoplasmic antibodies; *ATAQ*, Asthma Therapy Assessment Questionnaire; *FeNO*, fractional exhaled nitric oxide; *FEV1*, forced expiratory volume in 1; NA, data not available; *ppb*, parts per billion.

*Off of steroids on omalizumab.

†Asthma Therapy Assessment Questionnaire.