Improving Recognition and Management of EGPA

A Multidisciplinary Approach to Individualizing Treatment

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We would like to thank GlaxoSmithKline for making this event possible through the provision of an educational grant supporting this activity.

I invite you to follow along on the PDF slides you received.

Please feel free to submit questions via email to lisa.davis2@ascension.org

Agenda

- **MasterClass 1:** Recognizing and Diagnosing EGPA: What Are the Challenges?
- **MasterClass 2:** Individualizing Treatment for Patients With EGPA: Exploring Novel Therapeutic Options

After these presentations, we discuss a patient case that offers practical strategies for the diagnosis and management of EGPA within the context of a multidisciplinary approach

Be prepared to answer follow-up questions throughout the program, after the scientific sessions

Recognizing and Diagnosing EGPA

What Are the Challenges?

Churg-Strauss Syndrome (Allergic Granulomatosis and Angiitis)[1]

Originally described by pathologists Churg and Strauss (1951)

- 13 patients with a triad of asthma, hyper-eosinophilia, and vasculitis
- Histology: extravascular granuloma, tissue eosinophilia, and necrotizing vasculitis

1. Churg J, Strauss L. *Am J Pathol*. 1951;27:277-301.

What Is EGPA?[1]

EGPA (formerly known as the Churg-Strauss syndrome) is an eosinophilic disorder that can affect multiple organ systems

- **Moderate to severe asthma**

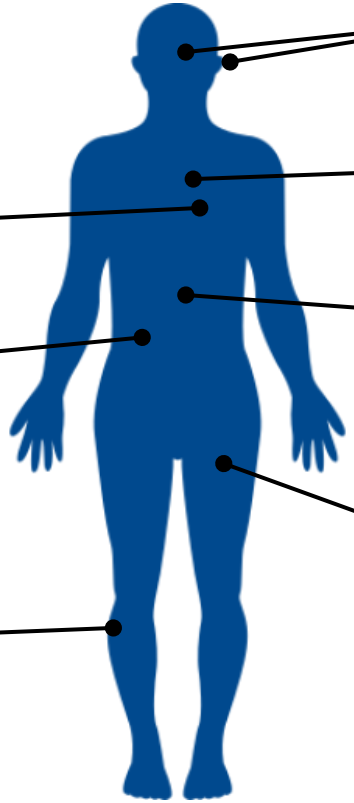
EGPA Is Characterized By …

- Paranasal sinus abnormality

- Extravascular eosinophils/ eosinophilic vasculitis
- Positive ANCA (30% to 40% of all patients)

1. Masi AT et al. *Arthritis Rheum.* 1990;33:1094-1100.

Clinical Presentation of EGPA Can Vary Greatly[1]



Otorhinolaryngologic System
- Neurosensory hearing loss
- Nasal polyps
- Sinusitis

Cardiac
- Pericarditis
- CHF, MI

Pulmonary
- Asthma
- Infiltrates
- Hemorrhage

Gastrointestinal
- Eosinophilic esophagitis
- Eosinophilic colitis

Renal
- Glomerulonephritis

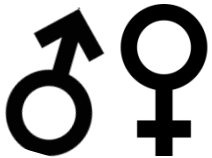
Skin
- Subcutaneous nodules
- Purpura

Nervous
- Peripheral neuropathy
- Mononeuritis multiplex

1. Lanham JG et al. *Medicine*. 1984;63:65-81.

EGPA: Whom Does It Affect?[1,2]

Equally affects men and women



Mean age at onset

48 years

Mean age at diagnosis

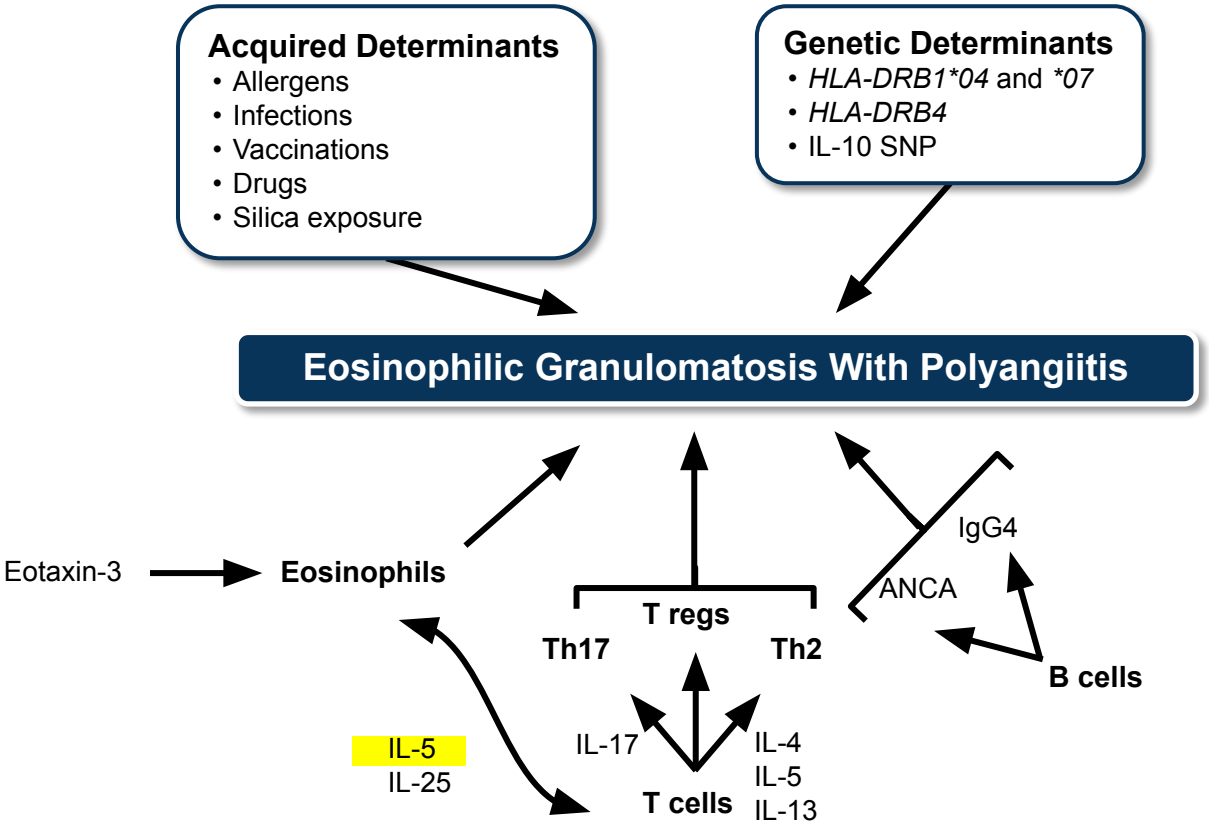
55 years

Although an understanding of what predicts disease onset remains poor, EGPA is likely the result of a complex interaction in which genetic and environmental factors lead to an inflammatory response

Principal players are eosinophils and T and B lymphocytes

1. Mouthon L et al. *J Autoimmun*. 2014;48-49:99-103.
2. Gioffredi A et al. *Front Immunol*. 2014;5:549.

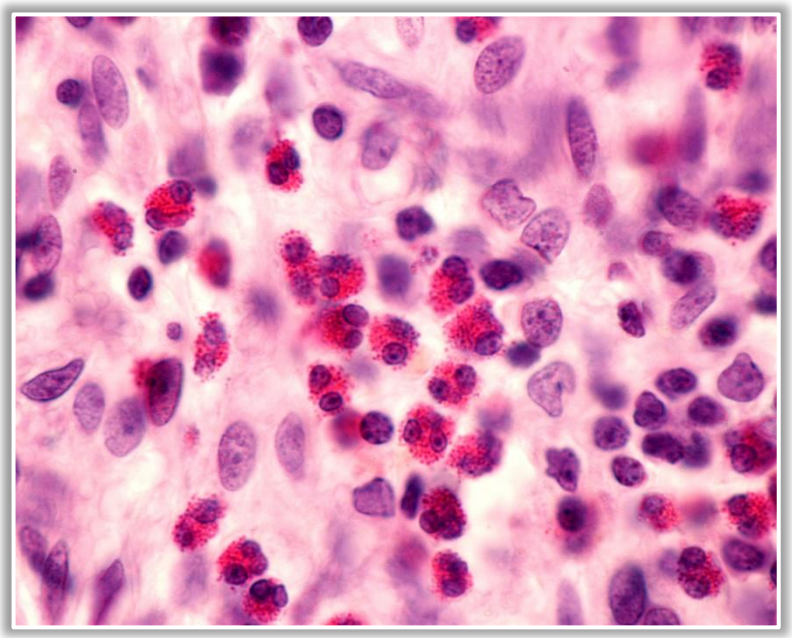
EGPA: Likely a Result of Complex Interactions Between Genetic and Environmental Factors[1]



1. Gioffredi A et al. *Front Immunol*. 2014;5:549.

Eosinophils Play a Major Role in the Pathophysiology of EGPA[1]

- Eosinophils cause tissue damage through release of cationic granule proteins
- Can cause organ damage mediated through associated fibrosis



1. Akuthota P et al. *Immunol Allergy Clin North Am*. 2015;35:403-411.

EGPA: Prevalence[1,2]

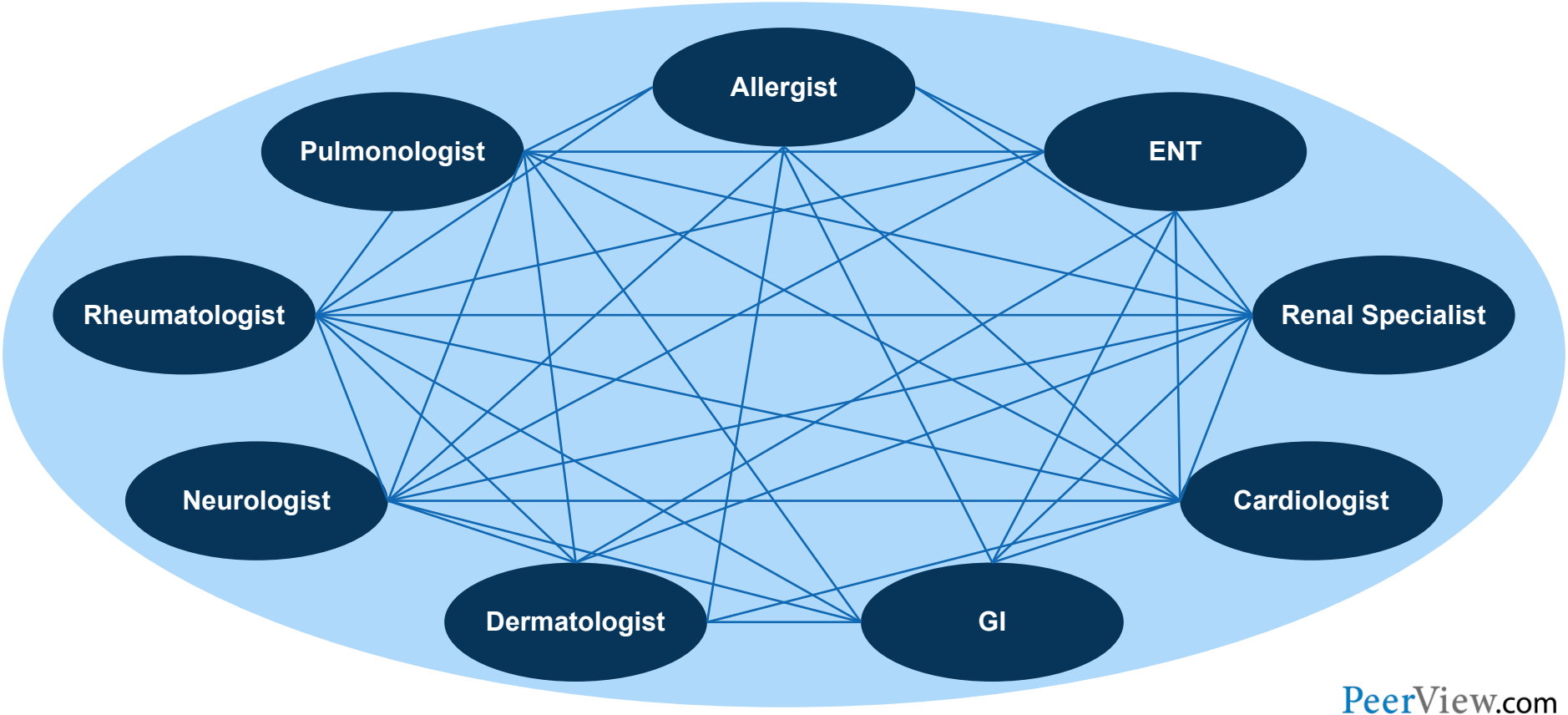
Estimated prevalence: about 14 cases per 1,000,000 individuals (about 5,000 people in the United States)

May be underestimated due to …

- Poor physician recognition
- Large numbers of patients who continue to be treated with systemic corticosteroids for “severe asthma” that is really EGPA
- New drugs that are able to quell EGPA symptoms, such as high-dose inhaled steroids

1. Mouthon L et al. *J Autoimmun*. 2014;48-49:99-103. 2. Gioffredi A et al. *Front Immunol*. 2014;5:549.

Importance of a Multidisciplinary Approach in EGPA



Differential Diagnosis of EGPA[1]

Onset	AEP	CEP	EGPA	HES
	Acute (Days)	Indolent (Weeks/Months)	Indolent (Weeks/Months)	Indolent (Weeks/Months)
Imaging	Diffuse	Peripheral	Patchy	Patchy
Fulminant respiratory failure	++	–	–	–
Asthma/allergy history	–	+	++	–
Smoking history	+	–	-	–
Vasculitis	–	–	++	–
ANCA	–	–	+	–
Cardiac involvement	–	+/-	+	++
Neurologic	–	+/-	++	++
Requires therapies other than GCs	–	–	+	++

Rare (-); occasional (+/-); common (+); occurs most of the time (++).

1. Wechsler ME. *Immunol Allergy Clin N Am*. 2007;27:477-492.

Diagnostic Criteria: EGPA

Lanham Diagnostic Criteria[1] (1984)

- Asthma
- Blood eosinophilia >1,500/mm^3 or >10% of total WBC
- Evidence of vasculitis involving ≥2 organs

American College of Rheumatology Classification Criteria[2] (1990)

- Asthma
- Eosinophilia (>10% of total WBC)
- Neuropathy
- Pulmonary infiltrates nonfixed
- Paranasal sinus abnormalities
- Extravascular eosinophils

Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides[3] (2012)

- Eosinophil-rich and necrotizing graunlomatous inflammation often involving the respiratory tract
- Necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia
- ANCA is more frequent when glomerulonephritis is present

1. Lanham JG et al. *Medicine.* 1984;63:65-81. 2. Masi AT et al. *Arthritis Rheum.* 1990;33:1094-1100. 3. Jennette JC et al. *Arthritis Rheum.* 2013;65:1-11.

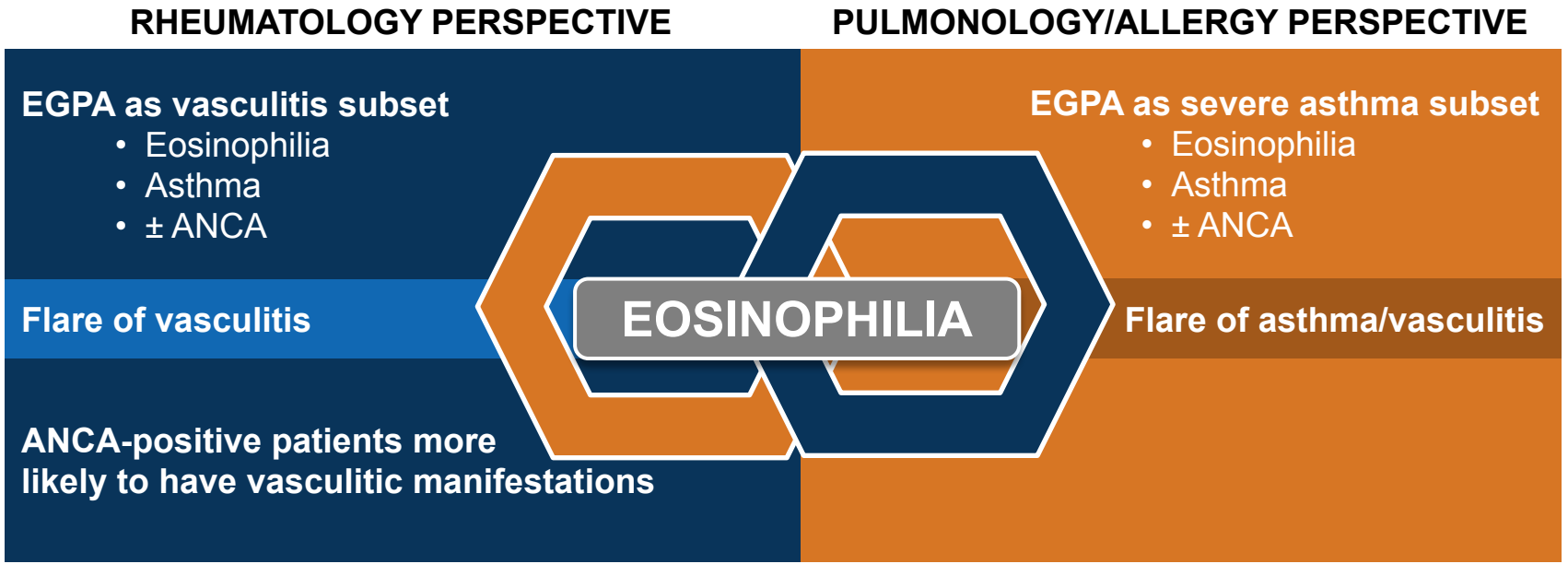
Diagnostic Criteria: EGPA Consensus Task Force[1]

Asthma plus eosinophilia (>1.0 x 10^9/L and/or >10% of leukocytes) plus at least two of the following

- A biopsy showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation
- Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)
- Pulmonary infiltrates, nonfixed
- Sino-nasal abnormality
- Cardiomyopathy (established by echocardiography or MRI)
- Glomerulonephritis (hematuria, red cell casts, proteinuria)
- Alveolar hemorrhage (by bronchoalveolar lavage)
- Palpable purpura

1. Wechsler ME, Akuthota P, et al. *N Engl J Med*. 2017;376:1921-1932.

EGPA From Rheumatology vs Pulmonology Perspective



EGPA: Clinical Course

Classically evolves in a phasic, developmental pattern[1]

Stage 1: Prodromal

- Initial allergic diathesis (usually allergic rhinitis), progressing into asthma
- May precede systemic disease by many years[2,3]

Stage 2: Eosinophilic

- Peripheral blood eosinophilia, eosinophilic infiltration in various organs[2,3]

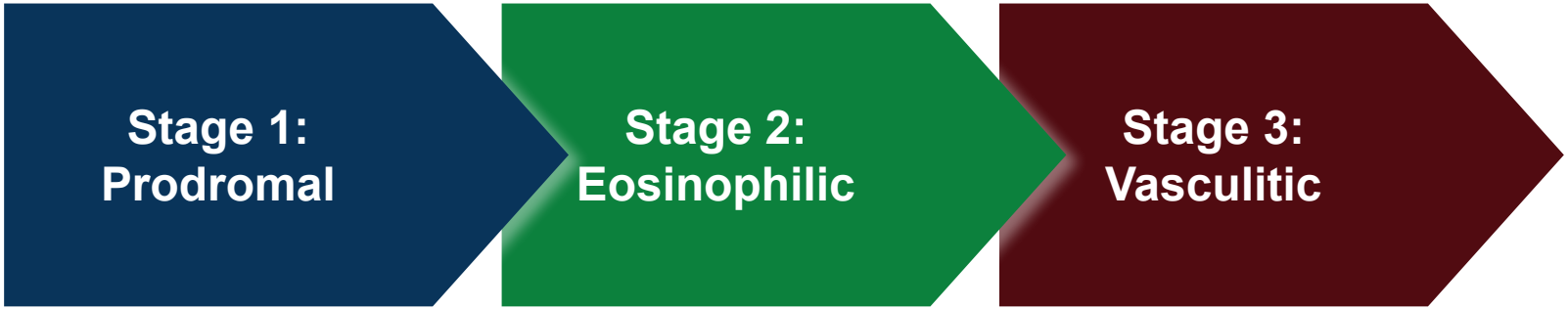
Stage 3: Vasculitic

- Terminal vasculitis stage: necrotizing vasculitis and granuloma formation[3]

1. Lanham JG et al. *Medicine.* 1984;63:65-81. 2. Vaglio A et al. *Allergy.* 2013;66:261-273. 3. Baldini C et al. *Rheum Dis Clin North Am.* 2010;36:527-543.

EGPA: Clinical Course (Cont'd)

However, EGPA does not always follow this pattern in the real world; stages may overlap[1,2]



- Mostly develops over years, but it can develop over months
- Patients often experience nonspecific constitutional symptoms
  - Malaise, weight loss, fever, myalgia[3]

1. Noth I et al. *Lancet.* 2003;361:587-594. 2. Vaglio A et al. *Allergy.* 2013;68:261-273. 3. Baldini C et al. *Rheum Dis Clin North Am.* 2010;36:527-543.

Laboratory Findings: Diagnosis[1]

Eosinophilia >10% or 1,000 (absolute eosinophil count)

- Responds quickly to therapy

Increased ESR, CRP, IgE, RF, ANA

P-ANCA positivity: 30% to 40% of all patients

- Associated with renal involvement, neuropathy, and biopsy-proven vasculitis

1. Sable-Fourtassou R et al. *Ann Intern Med.* 2005;143:632-638.

Can EGPA Be Diagnosed Without Vasculitis?

- ✔ Don’t need definitive biopsy
- ✔ Must have blood eosinophilia!
- ✔ Should have tissue eosinophilia
- ✔ Can use surrogate markers: ANCA, EMG
- ✔ Should have asthma and some evidence of extrapulmonary involvement
- ✔ If no definitive vasculitis, this could be possible or probable EGPA; need to follow closely and monitor for vasculitis

Individualizing Treatment for Patients With EGPA

Exploring Novel Therapeutic Options

Goals of Treatment

- Limit disease-related damage and treatment-related morbidity
- Prevent relapse
- Reduce toxicity of induction therapy

Management and Treatment of EGPA[1]

Treatment plan may vary depending on patient presentation

For Patients With Organ- or Life-Threatening Manifestations

Intensive therapy with glucocorticoids (1 mg/kg/d) and cyclophosphamide (or rituximab)

For Patients With Mild to Moderate Disease

Lower doses of glucocorticoids

Remission Maintenance

Methotrexate, azathioprine, anti–IL-5 therapy

Managing Asthma and Sinus Disease

- Bronchodilators and inhaled steroids
- Nasal steroids
- Anti-IgE therapy/anti–IL-5 therapy

1. Groh M et al. *Eur J Intern Med*. 2015;26:545-553.

Monitoring/Follow-Up of Patients

Laboratory
(EOS, CRP, ESR, kidney disease especially in ANCA+ patients, drug toxicities)

Imaging, particularly in initial infiltrative disease

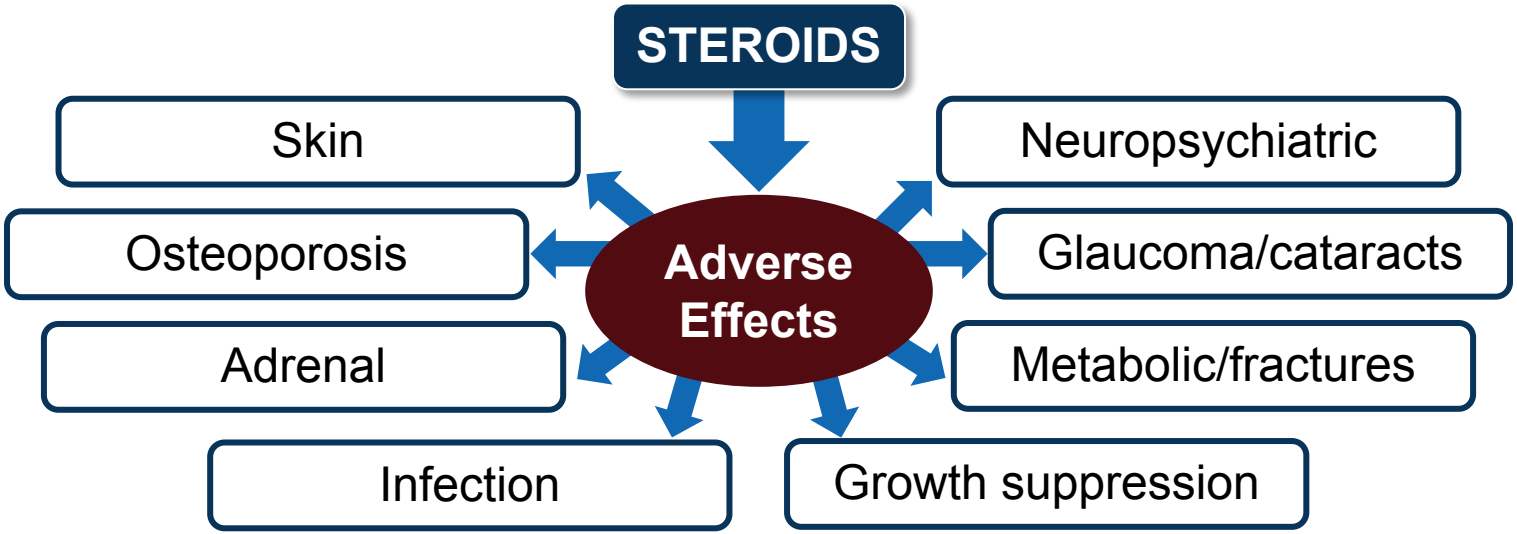
Pulmonary function testing

Emphasize to patients to be vigilant for any new signs or symptoms!

Treatment of EGPA

- Steroids remain the mainstay of treatment because they effectively and quickly treat asthma and upper-airway and lower-airway disease, and stop the process of vasculitis

However …



Management With Steroids

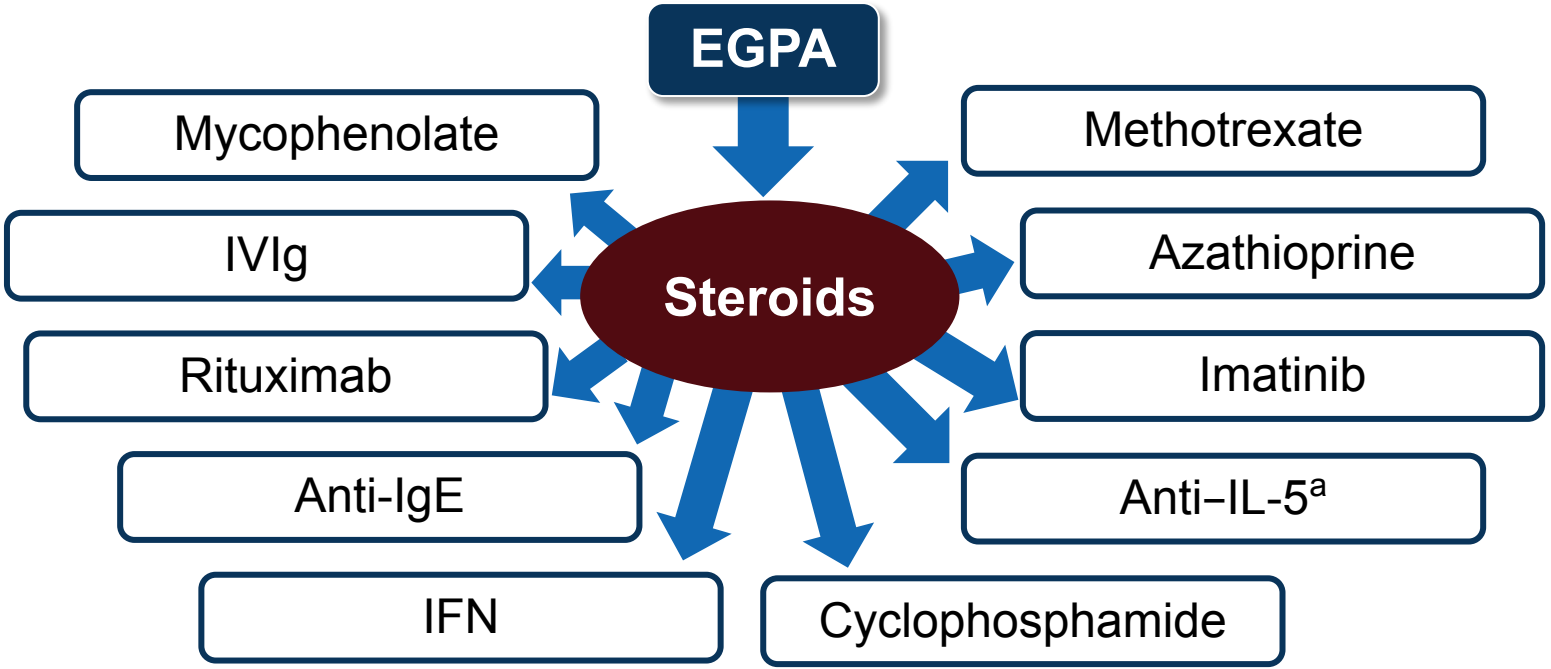
Patients with milder disease may be candidates for steroid monotherapy

ie, five-factor score = 0 or 1	No kidney, GI, heart, or CNS involvement

However …

Disease often recurs with steroid withdrawal or lower doses	Need to taper slowly	Few patients are able to get off steroids	Not all patients respond to steroids initially

EGPA Treatment After Steroids[1]



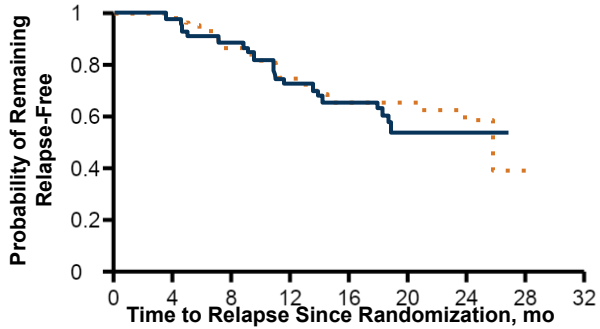
[a] Only FDA-approved agent for EGPA.

1. Groh M et al. *Eur J Intern Med*. 2015;26:545-553.

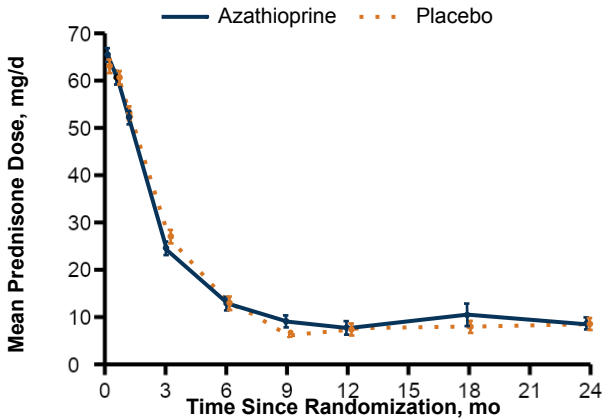
Azathioprine in EGPA[1]

Addition of azathioprine to steroids for patients with nonsevere vasculitis had no significant benefit

- No decrease in treatment failures
- No decrease in relapse rate
- No decrease in steroid use
- No improvement in asthma/ sinus manifestations



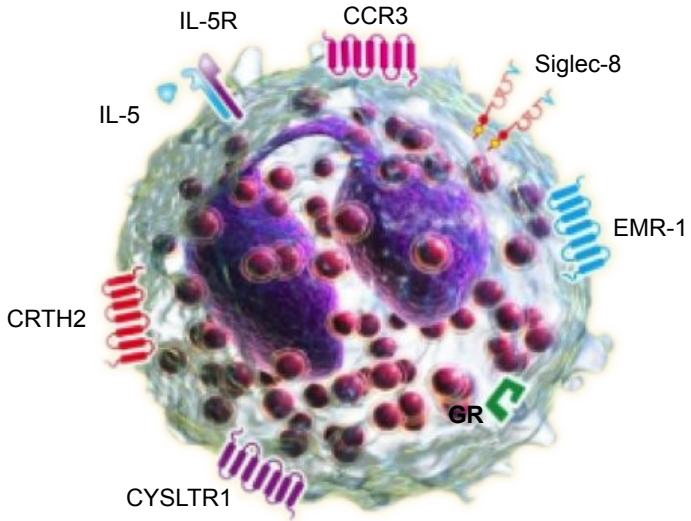
Azathioprine	44	43	39	30	27	21	12	0	–
Placebo	43	42	37	32	28	26	13	1	0



1. Puéchal X et al. *Arthritis Rheumatol*. 2017;69:2175-2186.

Targeting Eosinophils[1]

- The eosinophil possesses multiple targets that are the focus of active research in patients with hypereosinophilic diseases
  - **IL-5**
  - CCR3
  - Siglec-8
  - EMR1
  - CRTH2
  - Cysteinyl leukotriene 1
  - Glucocorticoid receptor



1. Wechsler ME et al. *J Allergy Clin Immunol*. 2012;130:563-571.

Targeting IL-5 for the Treatment of EGPA[1,2]

IL-5 is an eosinophil-specific cytokine

Plays a central role in

- Proliferation and maturation of eosinophil progenitors
- Trafficking of eosinophils from bone marrow to blood to tissue
- Survival of mature eosinophils

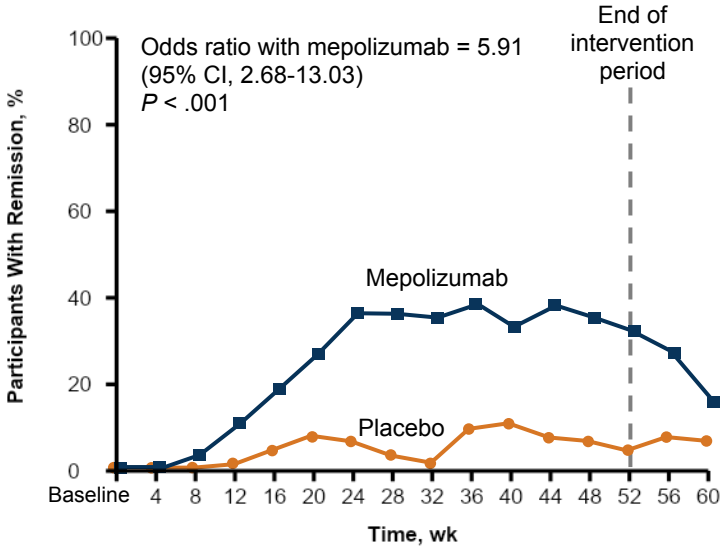
Targeting IL-5 with a monoclonal antibody can reduce circulating eosinophilia and, to a certain extent, tissue eosinophilia

Mepolizumab, already approved for severe eosinophilic asthma in 2015, was FDA-approved in 2017 as treatment for EGPA in adult patients

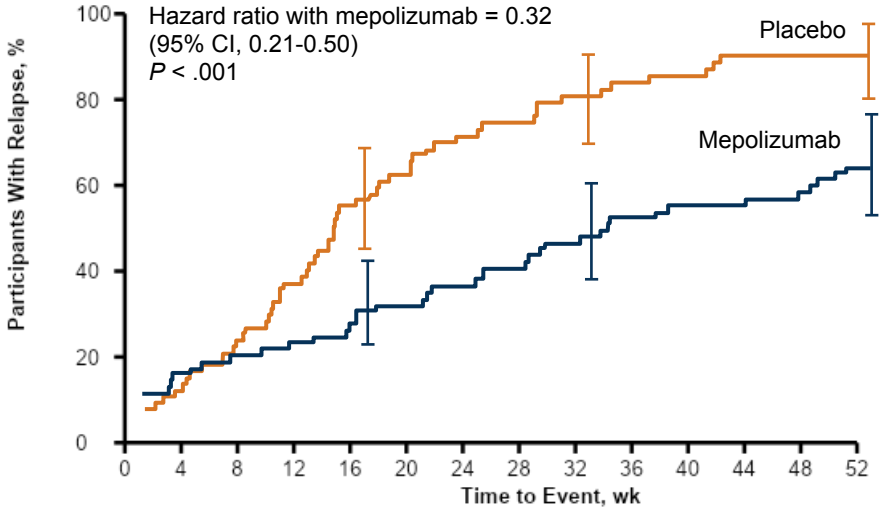
1. Roufosse F. *Front Med*. 2018;5:49. 2. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-eosinophilic-granulomatosis-polyangiitis-rare-disease-formerly-known-churg.

IL-5 Targeted Therapy for EGPA: Mepolizumab[1]

Remission



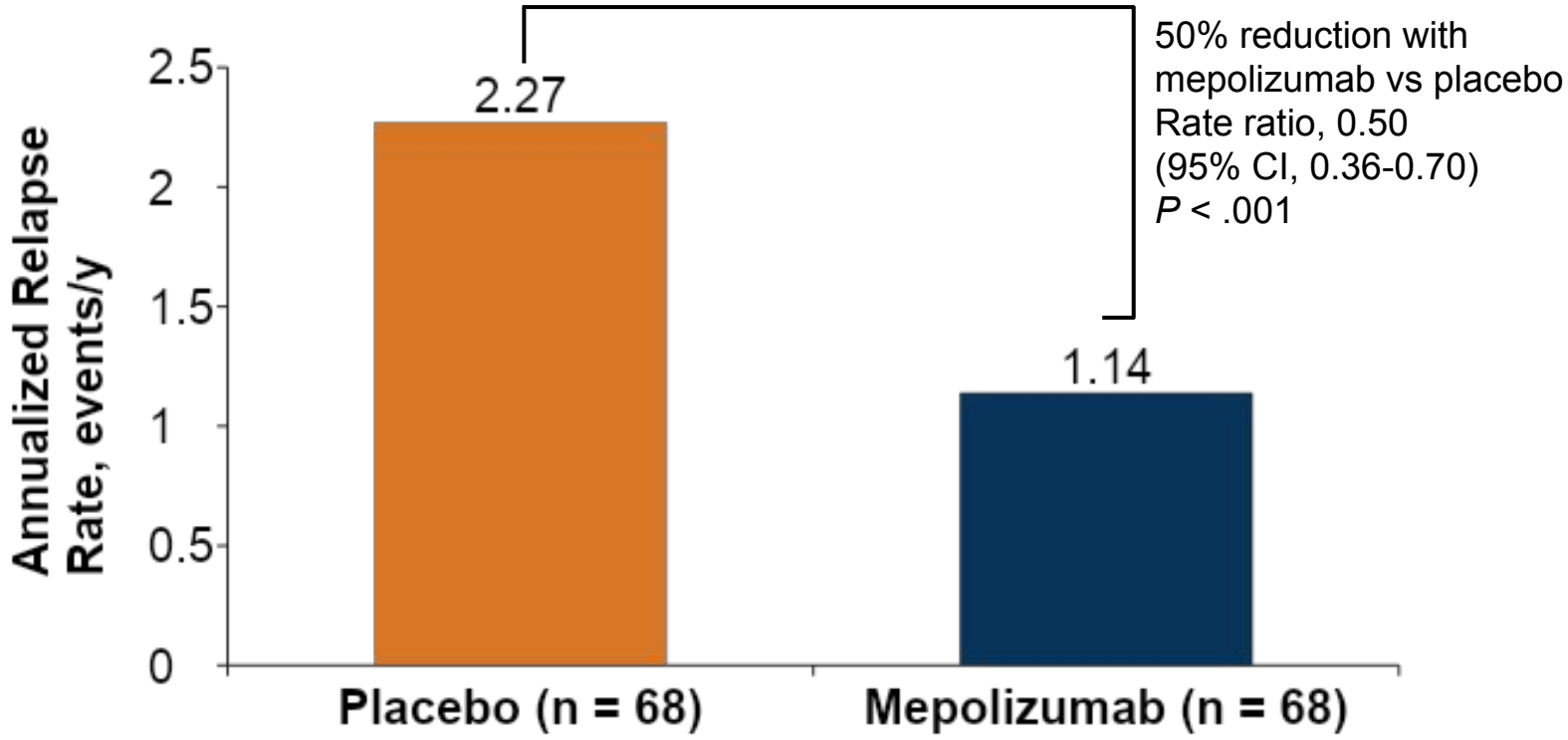
Relapse



No. at Risk	6			
Mepolizumab	68	55	43	25
Placebo	68	33	16	9

1. Wechsler ME et al; EGPA Mepolizumab Study Team. *N Engl J Med*. 2017;376:1921-1932.

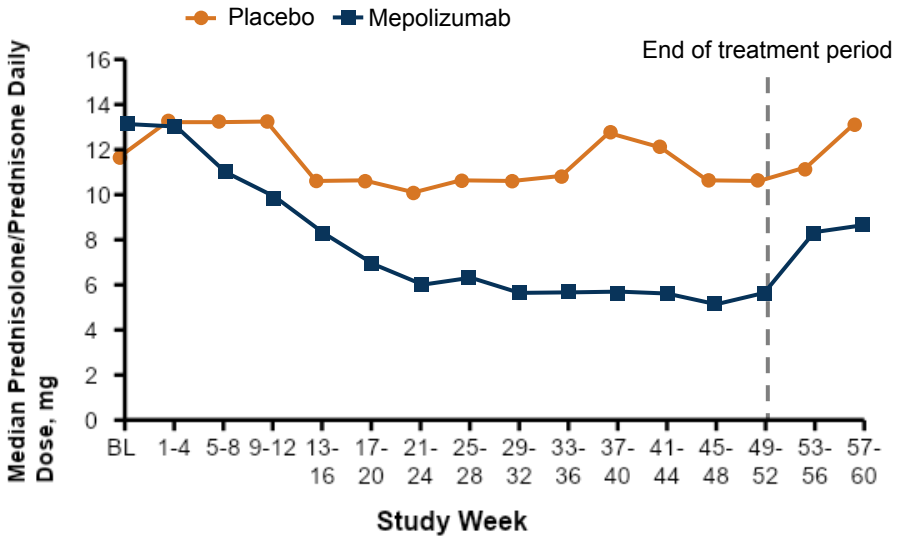
IL-5 Targeted Therapy for EGPA: Mepolizumab[1] (Cont'd)



1. Wechsler ME et al; EGPA Mepolizumab Study Team. *N Engl J Med*. 2017;376:1921-1932.

Steroid Reduction With Mepolizumab[1]

57% of patients treated with mepolizumab achieved ≥50% reduction in daily OCS compared with 21% in placebo arm



Daily prednisolone/prednisone dose during weeks 48-52.
Analysis in ITT population.

1. Wechsler ME et al; EGPA Mepolizumab Study Team. *N Engl J Med*. 2017;376:1921-1932.

Emerging Anti–IL-5 Therapies

Reslizumab (Phase 2)[1]

- In 7 patients with EGPA, all with extrapulmonary involvement, after 48 wk of treatment, all patients had a >50% reduction in prednisolone dose
- 5 (71%) reduced below the 7.5 mg/d threshold deemed consistent with remission by EULAR

Benralizumab (Phase 3)[2]

- In 10 patients with EGPA >50% reduction in steroid dose

Granted FDA orphan drug designation for EGPA in 2018

1. Kent BD et al. *Thorax*. 2018;73:A176. 2. https://clinicaltrials.gov/ct2/show/NCT04157348.

Emerging Therapies in the Treatment of EGPA

Omalizumab (anti-IgE)[1]	• Appears to be steroid sparing • Reduction in asthma exacerbations/hospitalizations, improvement in FEV_1, no decrease in eosinophil count
Rituximab[2]	• Some efficacy • Reduction in steroid requirement, but relapses remained high • ANCA+ patients had longer asthma/ENT relapse–free time and shorter time to remission
Dexpramipexole[3]	• Depletes eosinophils (oral steroid-sparing agent)
Anti–siglec-8[4]	

1. Sozener ZC et al. *World Allergy Organ J*. 2018;11:39. 2.Teixeira V et al. *RMD Open*. 2019;5:e000905. 3. Panch SR et al. *Blood*. 2018;132:501-509.
4. Carroll DJ et al. *J Allergy Clin Immunol*. 2018;141:2196-2207.

Conclusions

- Recognize the signs of EGPA, take note of high eosinophil counts on lab workup, and collaborate in treatment and long-term follow-up
- Although EGPA has significant morbidity, prognosis has greatly improved
- Progress in the understanding of EGPA has provided novel and emerging treatment options
- Steroids are first-line therapy but are associated with significant side effects and toxicity
- Consider biologics and cytotoxic therapy in patients with
  - Steroid-refractory disease
  - Step-down therapy
  - Relapse

As newer therapies emerge and advances in EGPA continue, clinicians will have more tools to better diagnose, treat, and care for patients

Practicum

Case Presentation

A 56-year-old white man with a 30-year history of asthma; in addition, he has …

- ✓ Hypertension
- ✓ Hyperlipidemia
- ✓ History of COPD secondary to paint exposure (due to his previous occupation)

- He notes that 8 months earlier, as he was trying to clean dusty shelves at his place of employment, he needed to visit a walk-in clinic, after which his asthma attacks began occurring on a regular basis

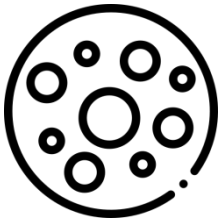
- His asthma attacks were treated with prednisone, but when the prednisone was tapered, the asthma came back

Case Presentation (Cont'd)

- 8 months after his asthma attacks began occurring with regularity, the patient developed emesis and a high fever, which he treated with loperamide and acetaminophen

- In the same month, he was hospitalized for pneumonia and a new lower extremity rash in the setting of eosinophilia and leukocytosis
  - He received antibiotic treatment; his lower extremity exanthem was believed to be due to an insect bite or a drug exposure
- Hospitalized again in the same month for sudden pain that he developed in the left lower extremity, which he described as a shooting, burning, and throbbing pain

Case Presentation (Cont'd)



Rash on his legs, hives on his face, and purpura on his lower extremities developed within 2 days of rehospitalization

MRI demonstrated degenerative disk disease at L4-L5 and L5-S1, with mild broad disk protrusion at L5-S1, with a mild mass effect on the thecal sac

Neurologic evaluation: "difficult to distinguish vasculitis from nerve impingement"; outpatient follow-up recommended

Case Presentation (Cont'd)

Rheumatologic Evaluation

Rash believed to be consistent with leukocytoclastic vasculitis

Prednisone 30 mg for 1 week was given followed by a prednisone taper

Case Presentation (Cont'd)

Continued pain in left lower extremity and difficulty ambulating

Ankle brachial index 1.27 on right and 1.31 on left

Original rash decreased but persisted

Test Results

- EOS: 26.5%, absolute EOS count 3,950
- Hepatitis A, B, and C tests negative
- Skin biopsy showed small vessel vasculitis or prominent EOS
- ANCA negative
- IgE 1933, CRP 11.04, ESR 29
- RA factor +

Case Presentation (Cont'd)

- ✔ Treated with cyclophosphamide 2 mg/kg PO and prednisone 1 mg/kg followed by taper
- ✔ As prednisone was tapered, asthma gradually came back (uncontrolled with inhalers)
- ✔ Started treatment with mepolizumab 300 mg 1x/month
- ✔ 3 months later, completely off steroids
  - On azathioprine and mepolizumab
- ✔ Continues to have foot drop (unprogressed), neuropathy hasn't moved to other extremities

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Abbreviations

- AEP: acute eosinophilic pneumonia
- ANCA: antineutrophil cytoplasmic antibodies
- CCR3: C-C motif chemokine receptor 3
- CEP: chronic eosinophilic pneumonia
- CRP: C-reactive protein
- CYSLTR1: cysteinyl leukotriene receptor 1
- EGPA: eosinophilic granulomatosis with polyangiitis
- EMG: electromyography
- ENT: ear, nose, and throat
- EOS: eosinophil
- ESR: erythrocyte sedimentation rate
- EULAR: European League Against Rheumatism
- GC: glucocorticoid
- GR: glucocorticoid receptor
- HES: hypereosinophilic syndrome
- *HLA-DRB1*: major histocompatibility complex, class II, DR beta 1
- *HLA-DRB4*: major histocompatibility complex, class II, DR beta 4
- IFN: interferon
- IgE: immunoglobulin E
- IgG4: immunoglobulin G4
- IL-4: interleukin 4
- IL-5: interleukin 5
- IL-10: interleukin 10