Northwestern Medicine®

Clinical Work-up and Management of Hypereosinophilic Syndromes (HES)

Fei Li Kuang, MD-PhD
Assistant Professor
Division of Allergy Immunology

Illinois Society Allergy Asthma Immunology
April 23th, 2023

Disclosures

I receive industry funding from AstraZeneca, the manufacturer of benralizumab (Fasenra), to study predictors of response in HES with benralizumab treatment

I received advisory board fees from GlaxoSmithKline, the manufacturer of mepolizumab (Nucala), to discuss the overlap between EGPA and HES

I will be discussing off-label use of medications for the treatment of HES

Lecture Objectives

- Evaluation of hypereosinophilia

- Review the clinical subtypes of hypereosinophilic syndromes

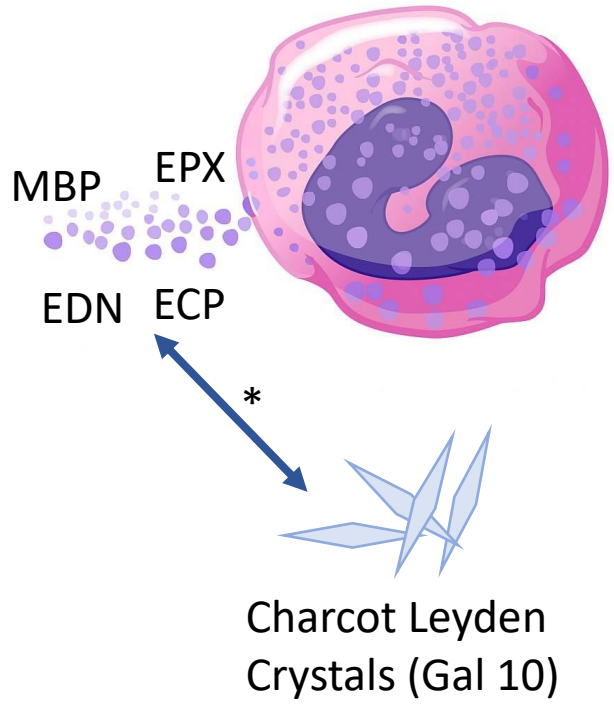
- Discuss current and future HES treatments

    - *Lessons we are learning from people without eosinophils*

Eosinophils in Human Biology and Disease

- Tissue dwelling and circulating granulocytes
- Eosin-staining granules contain cytotoxic proteins
  - “degranulate” release contents or free granules

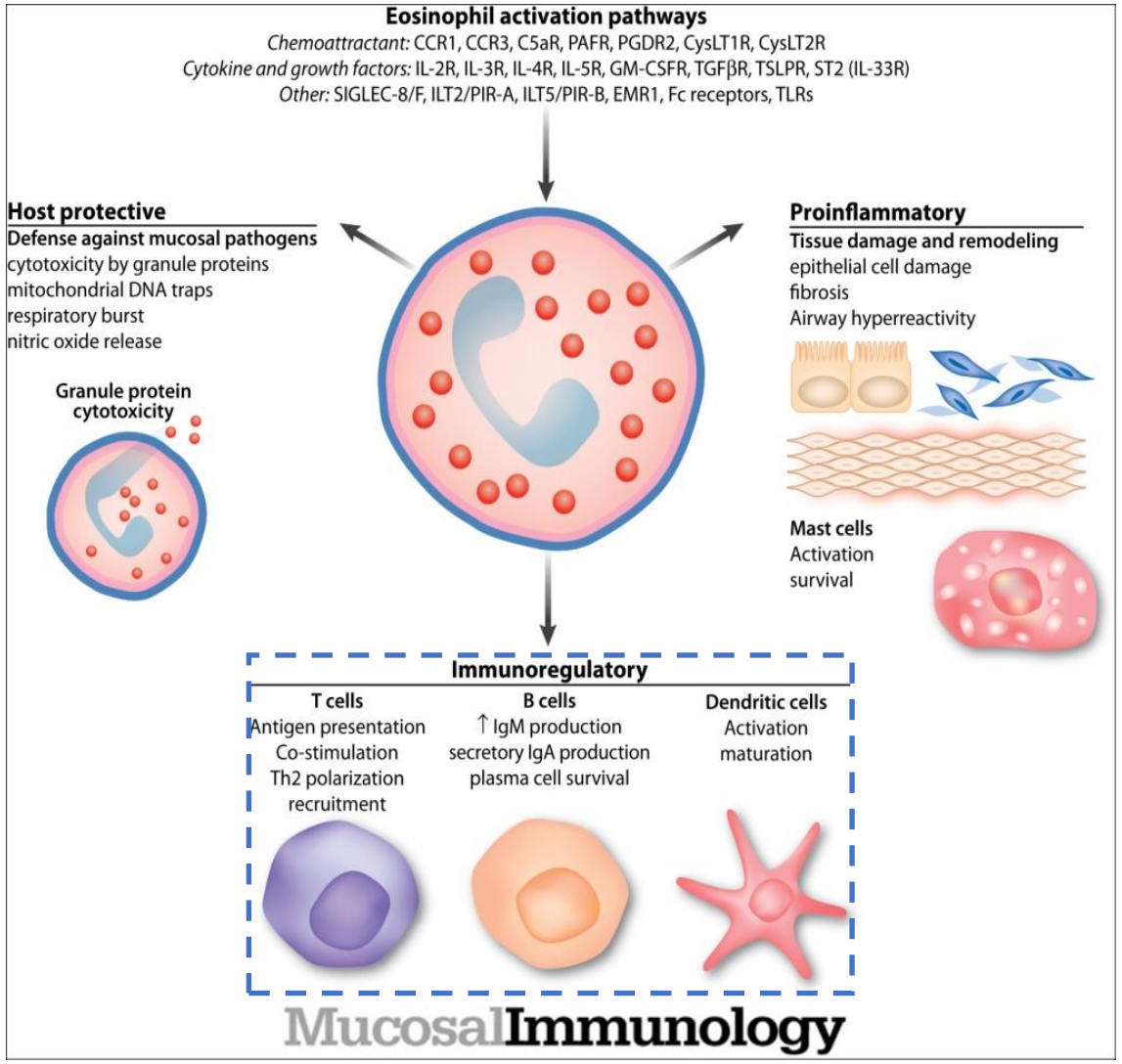
- Host defense role in parasitic infection
- Pathogenic (?) role in a variety of allergic and inflammatory diseases



Are eosinophils instigators or bystanders in disease pathogenesis?

*Grozdanovic et al. JACI 2020

Homeostatic and Immunoregulatory Roles for EOS?



- Immunomodulation
- Plasma cell homeostasis
- Vaccine recall response
- Metabolic regulation
- Tumor surveillance

Mucosal Immunology (2015) **8**, 464-475;

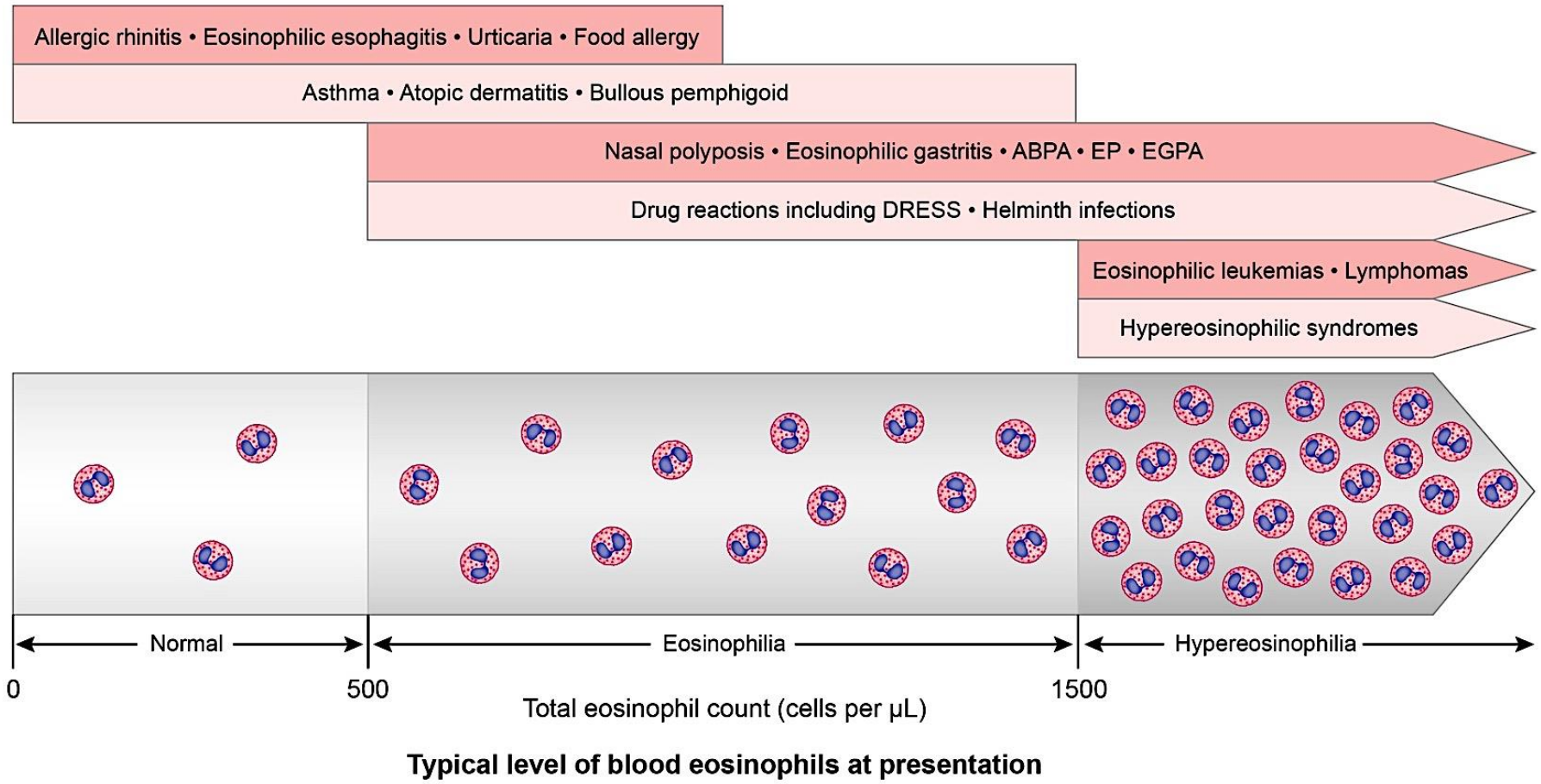
Common causes of eosinophilia

Types of Disorders	Specific Examples
Atopic Diseases	Asthma, Atopic Dermatitis* Allergic Rhinitis, Chronic Rhinosinusitis with Nasal Polyps* Allergic Bronchopulmonary Aspergillosis* Eosinophilic Pneumonia*
Drug Reactions* (incl. DRESS)	Antibiotics, anti-epileptics, allopurinol
Gastrointestinal Disorders	Eosinophilic Esophagitis (EoE), Eosinophilic gastritis/duodenitis (EG/ED)* Eosinophilic colitis (EC)*
Infections*	Parasitic diseases (esp. helminths)
Immunodeficiencies*	IPEX, Hyper-IgE syndrome, Omenn syndrome DOCK8 deficiency
Malignancies*	Lymphoma, leukemia, solid tumors
Autoimmune	Bullous pemphigoid Eosinophilic granulomatosis polyangiitis*

* Can present with hypereosinophilia

Adapted from Guo and Bochner Allergy Asthma Proc 40:429-432, 2019

Diagnosis: eosinophilia vs. hypereosinophilia

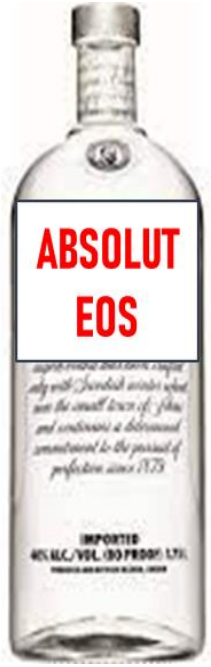


Typical level of blood eosinophils at presentation

EOS LEVELS AT PRESENTATION MAY BE SUPPRESSED DUE TO STEROIDS

Bochner Ann Allergy Asthma Immunol. 121:150-155, 2018

Hypereosinophilic Syndromes (HES)



Persistent AEC ≥ 1,500 cells/µL = HE - hypereosinophilia

Persistent AEC ≥ 1,500/µL +

Clinical symptoms related to eosinophils = **HES**

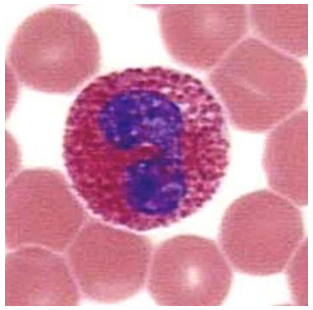
No longer require "≥ 6 months duration" but the AEC should be elevated "on more than one occasion."

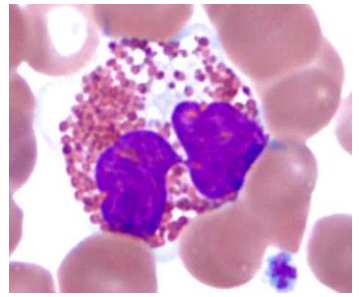
(Klion et al. JACI 2006; Simon et al. JACI 2010; Valent JACI 2012)

Image modified from https://www.absolut.com/us/

Clinical Subtypes of HES

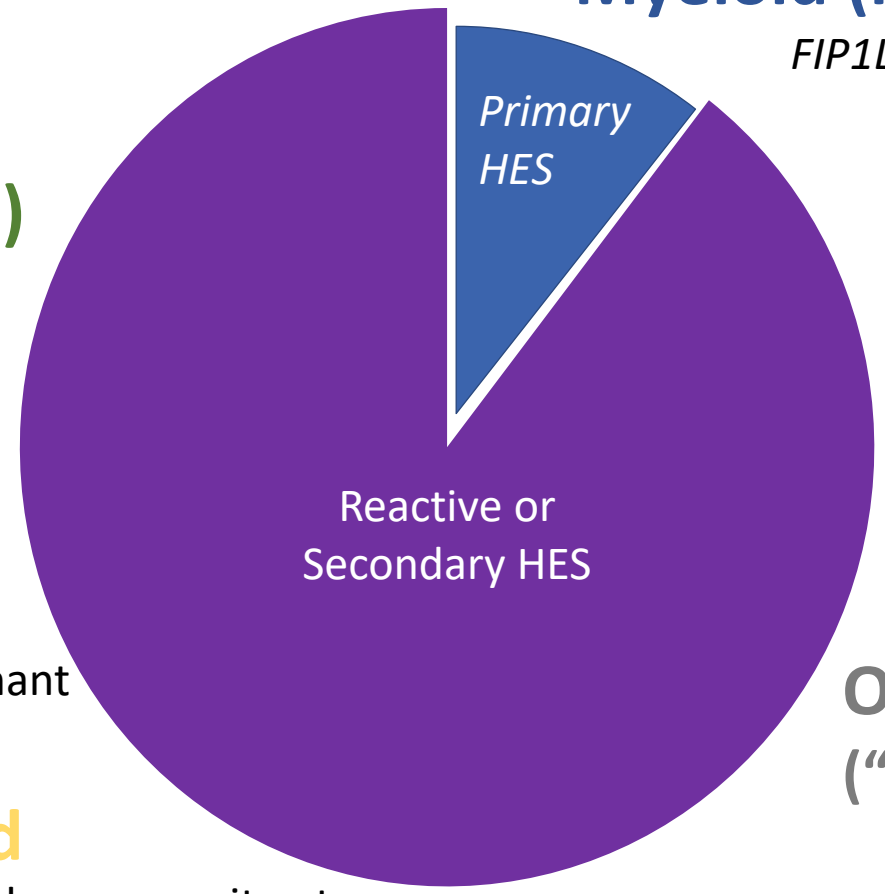
NIH COHORT (n=505)





Myeloid (MHES)

FIP1L1/PDGFRA (>80%)



Idiopathic (iHES)

Lymphoid (LHES)

CD3-CD4+ aberrant T cell population

Familial

Rare autosomal dominant

Associated

malignancy, drugs, parasite etc.

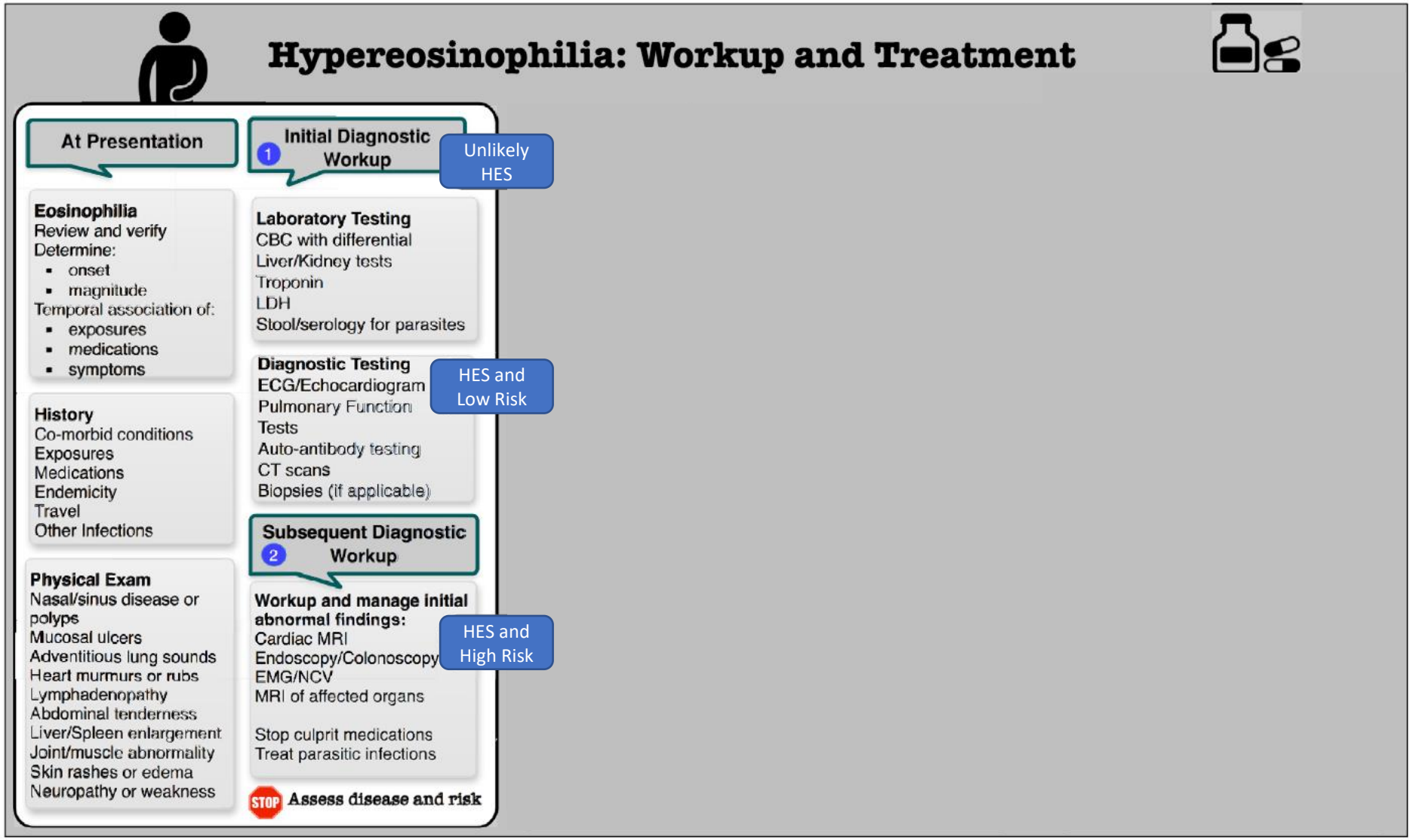
Overlap

("dual CITIZENSHIP")

Single-organ disease e.g. EGPA, CEP or

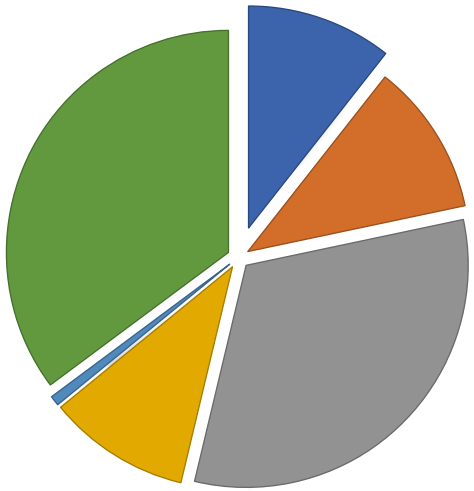
Eosinophilic GI disease

Data courtesy of Human Eosinophil Section, NIAID



Khoury and Bochner JACI-In Practice, 6:1446-1453, 2018

Myeloid HES (MHES)



KNOWN DEFECT
PDGFRA
PDGFRB
FGFR1
Other: JAK2, FLT3
NO KNOWN DEFECT
CEL but no defined genetics
WHO DEFINED MN-eo
BCR/ABL
JAK2 V617F
CBF-beat AML
MDS-eo

Primary HES

- *PDGFR*-positive MN (>80%) → Treat with Imatinib
- Chronic Eosinophilic Leukemia → BM transplant
- Other mutation-positive MN such as *JAK2*
- Idiopathic HES with myeloid features

Diagnostics/Features

- ↑vitamin B12 or serum tryptase
- Organomegaly

*Insensitive**

- Anemia, thrombocytopenia
- *FIP1L1-PDGFRA* translocation (aka CHIC2 FISH) in blood or bone marrow
- Bone marrow biopsy demonstrating dysplastic EOS, myelofibrosis

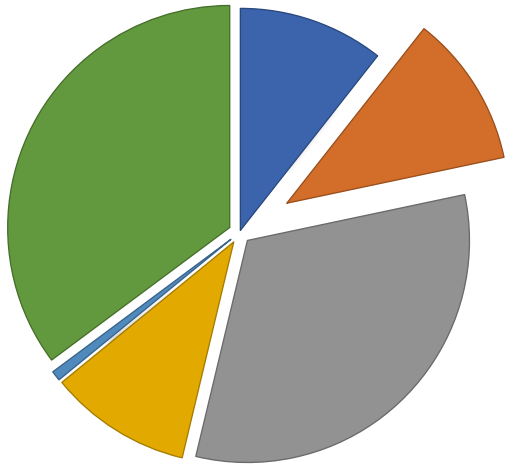
****Myeloid HES can be asymptomatic and are often corticosteroid insensitive**

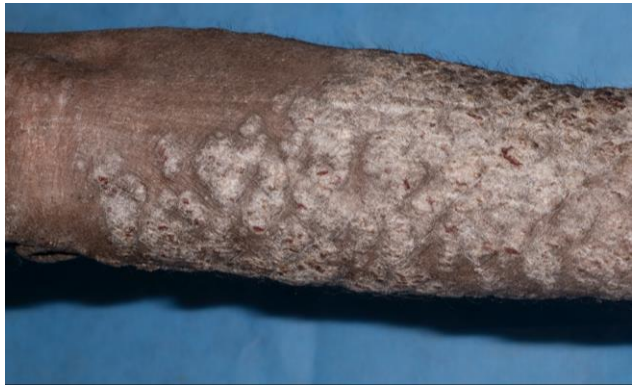
Patient AEC not always very high

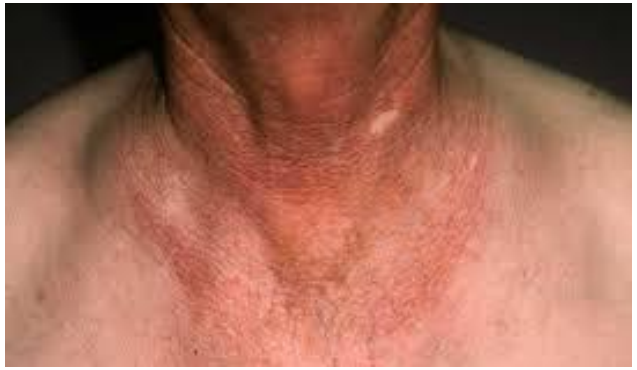
CHIC2 FISH can miss F/P disease

BUT MORTALITY is 30% at 3 years

*Klion et al. Blood 2003







Lymphoid HES (LHES)

- Aberrant T cell clone (majority CD3-CD4+) producing eosinophil-promoting cytokines like IL-5
- Often presents with skin manifestations (eczema, subcutaneous nodules, erythroderma) and/or angioedema;
- Adenopathy, DVTs, other organ manifestations

<u>Diagnostics</u>

- Flow cytometry – must specify:
  - **CD3-CD4+ population** or other aberrant T cell populations
  - CD3+CD4-CD8- (double negative)
  - CD3+CD4+CD8+ (double positive)
- Positive T cell receptor rearrangement (TCR) clone in blood and/or skin
- Increased total IgE (*insensitive) and serum TARC
- Bone marrow Bx: abundant but normal appearing EOS

****Lymphoid HES is associated with increased risk of lymphoma/leukemia**

*(Carpentier et al JACI 2021, Carpentier et al Front. Immunol 2020)
Images from NIAID/NIH

Overlap HES ("Dual Citizenship")

- Single-organ system involvement with peripheral eosinophilia, indistinguishable from HES
- Examples incl. **EGID**, EGPA, CEP

Treatment approach similar to "parent" disease

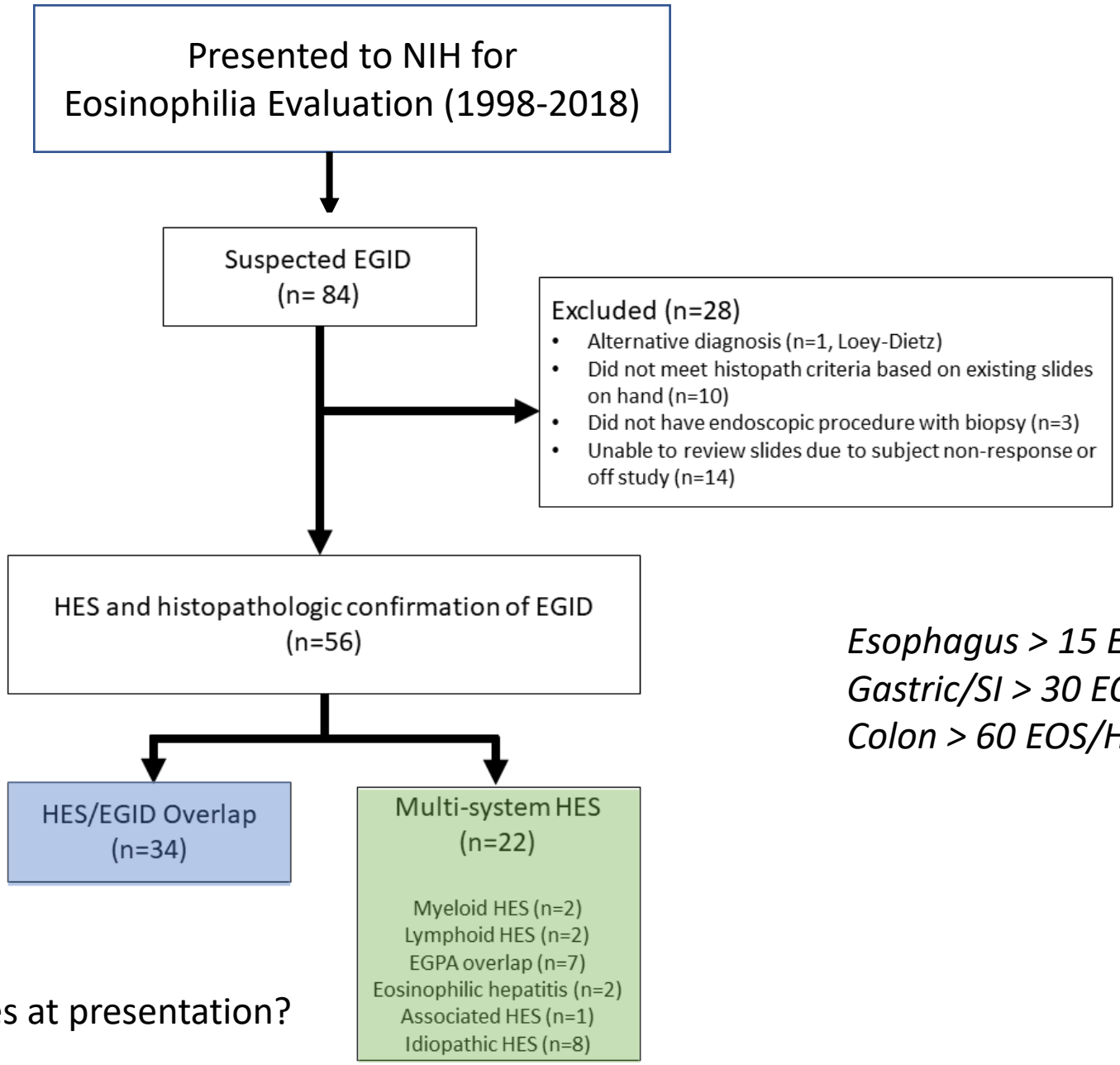
<u>Diagnostics</u>

- Same criteria as for "parent" disease

- Is bone marrow biopsy indicated?
- Will the patient go on to develop a "full-blown" HES?
- *One third of those with multi-system HES that included GI symptoms, was initially given a diagnosis of EGID alone***

****Monitor for development of other end organ manifestations**

**(Kuang et al JACI in Practice 2020)



Esophagus > 15 EOS/HPF
Gastric/SI > 30 EOS/HPF
Colon > 60 EOS/HPF

Retrospective Chart Review
- Pathologists
- Allergists
- Gastroenterologists

Are there different clinical features at presentation?

Kuang FL et al 2020 JACI in Practice

GI eosinophilia in the context of HES

HES/EGID Overlap – "single organ"

- GI symptoms + GI eosinophilia
- Hypereosinophilia (>1500 /μL)
- No other organ involvement

Multi-system HES with GI involvement

Often excluded from clinical studies for being "HES"

- GI symptoms + GI eosinophilia
- Hypereosinophilia (>1500 /μL)
- At least one other organ involvement

EGID/HES Overlap

Multi-system HES with GI

Are they distinct disease entities?

HES/EGID Overlap – "single organ"

- More likely to be treated with dietary therapy and topical steroids

Multi-system HES with GI involvement

- More likely to be treated with systemic corticosteroids
- Higher peak historic absolute eosinophil count in blood

No differences in co-morbid allergic diseases, types of GI symptoms or GI segment eosinophilia

Kuang FL et al 2020 JACI in Practice

One third of multi-system HES patients initially present with only GI symptoms

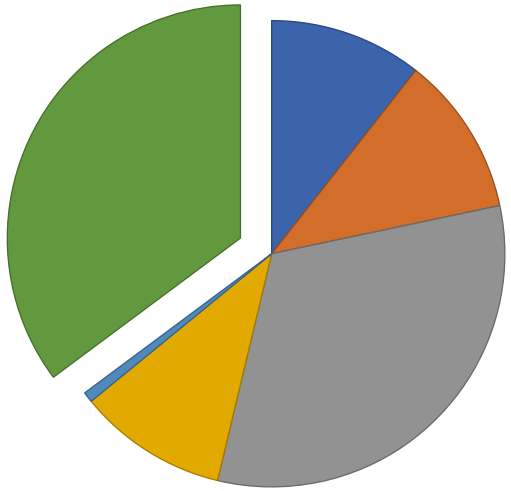
Eventual End-Organ Manifestations	Initial Presentation	
	Pure GI symptoms (n=8)	Multisystem or non-GI symptom presentation (n=14)

Median time to first non-GI symptom presentation is 1 year (range: 0.25 – 15 years)

Kuang FL et al 2020 JACI in Practice

Unusual Clinical Subtypes of HES

Idiopathic (iHES)



Familial HES

Autosomal dominant inheritance of HE, often without symptoms

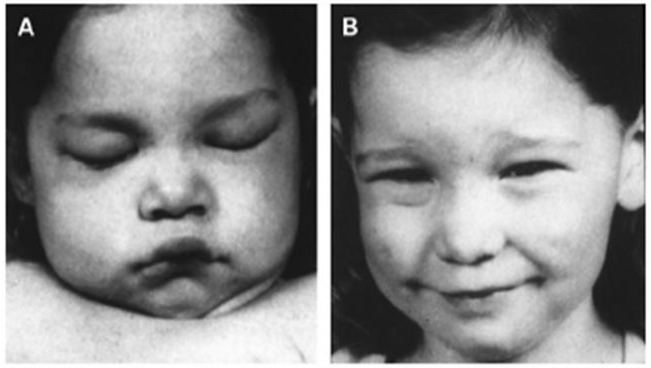
Associated HES

Diagnoses such as malignancy, drug reaction or parasitic infection (rare) with associated eosinophilia and clinical Sx

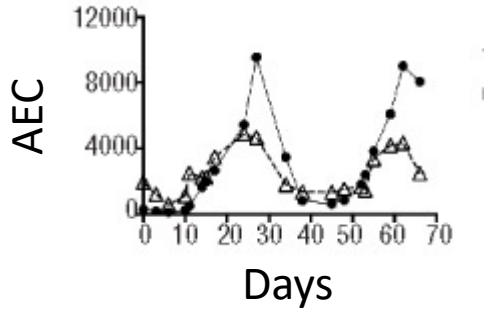
Episodic Angioedema with Eosinophilia

Spontaneous cyclical hypereosinophilia associated with skin rash, angioedema, weight gain
Self-resolution and no skin residua

- CD3negCD4pos T cell population
- Elevated IgM (>2 ULN)



(Katzen Am J Dis Child 1986)



(Khoury P et al Haematologica 2015)

Case 1 – Worsening asthma?

- 60 F with well-controlled AERD (on ASA, ICS-LABA)
- Subacute worsening of SOB → on 40 mg prednisone since Aug.
  - Sept - multiple OSH ICU admissions

    SOB and tachypnea → intubation for hypercapnic respiratory failure

    Responded to high dose steroids but quick re-admit when taper prednisone

  - Notable work up:

    CT Angio – negative for PE or infiltrates

    Troponin elevated → negative cardiac cath, normal EKG

    Infectious work up negative

    CBC notable only for AEC 1000 cells/μl on 40 mg prednisone

    CT Abd/Pelvis - **Small calcified R renal mass**

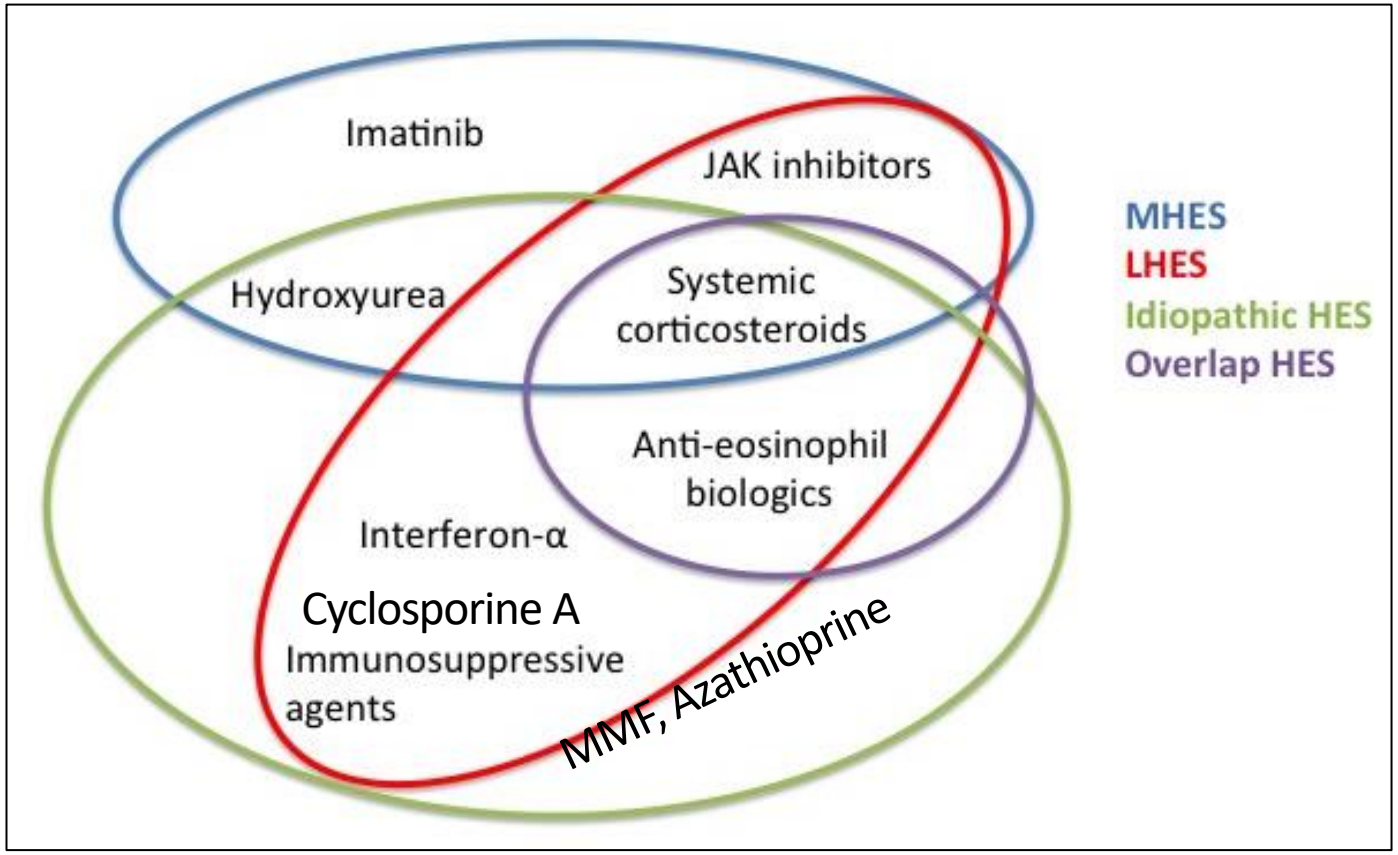
Case 1 – cont'd

- HES work up
  - Negative for lymphoid and myeloid HES, ANCA negative
  - TTE nl and cardiac MRI negative
  - AEC 100 - 400 cells/μl on 60 mg prednisone
  - Taken off aspirin to facilitate renal biopsy
- Prednisone <35 mg led to ED visit due to drop in peak flows, SOB and AEC 850
- Started on MEPO (anti-IL-5) for steroid sparing – able to get to 20 mg prednisone

- Renal biopsy results: renal cell carcinoma → underwent resection
- Came off steroids and mepolizumab

Working diagnosis: Associated HES

Treatments for HES



Imatinib and mepolizumab are the only FDA-approved drugs for HES

Khoury and Bochner JACI-In Practice, 6:1446-1453, 2018

Corticosteroids for HES

- First line therapy for all HES except Myeloid HES
  - 1 mg/kg is reasonable – prior experience with patient is more relevant
  - IV formulation if concern for absorption (GI disease)
  - Maximize topical corticosteroid therapy
- Check symptoms and CBCd regularly with steroid dose taper

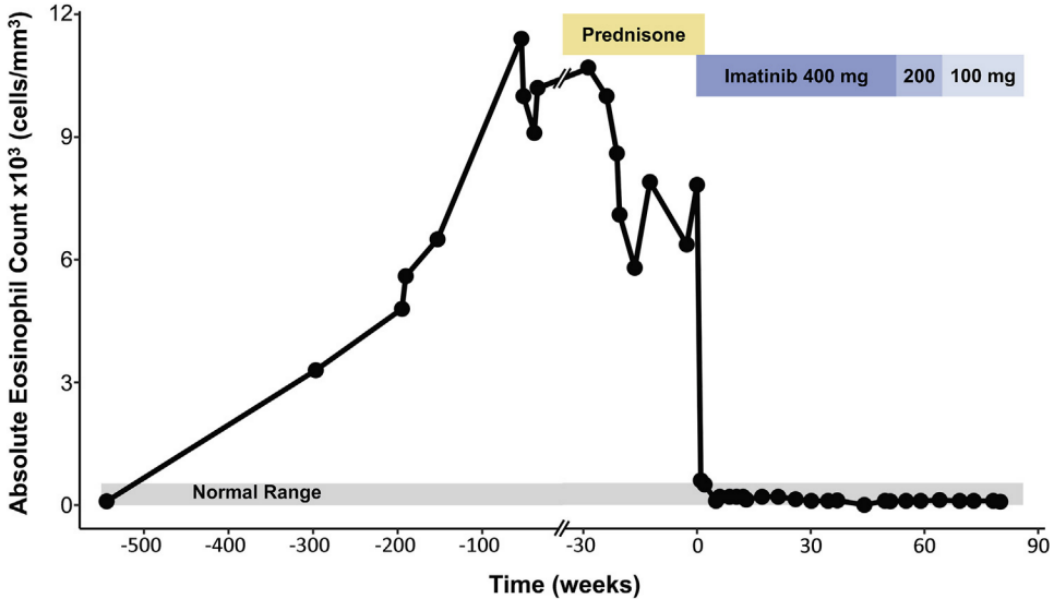
- Rebound of Sx and EOS can happen with abrupt tapering
- At < 10 mg prednisone, consider slow down taper
- Bridge to steroid-sparing agent if need prednisone > 10 mg (don't abruptly stop)
- Watch for side effects – avascular necrosis, diabetes, cataracts, adrenal insufficiency, osteoporosis, psychiatric issues, weight gain etc etc…..

Image from https://medshadow.org/need-know-corticosteroids/

Case 2 - EGID?

- 32 M c/o abdominal pain and diarrhea in 2012
- Diagnosed with EGID when eosinophilic infiltration of esophagus, TI and colon demonstrated on EGD/C-scope
- Treated with budesonide and cromolyn – persistent symptoms and AEC 4800 cells/mm^3
- Work-up: tryptase: 56.1 Vitamin B12: 1367 *FIP1L1-PDGFRA* FISH - negative
- Flow cytometry – negative, parasitic work up negative
- BM Bx:
  - Scant marrow with increased EOS
  - CD25+ MC suggestive but not diagnostic of SM
  - Blood reportedly negative for D816V KIT
- Treated with Prednisone 20-50 mg daily in 2017 but with persistent symptoms and AEC 5800 to 10,700 cells/mm^3

Case 2, cont'd



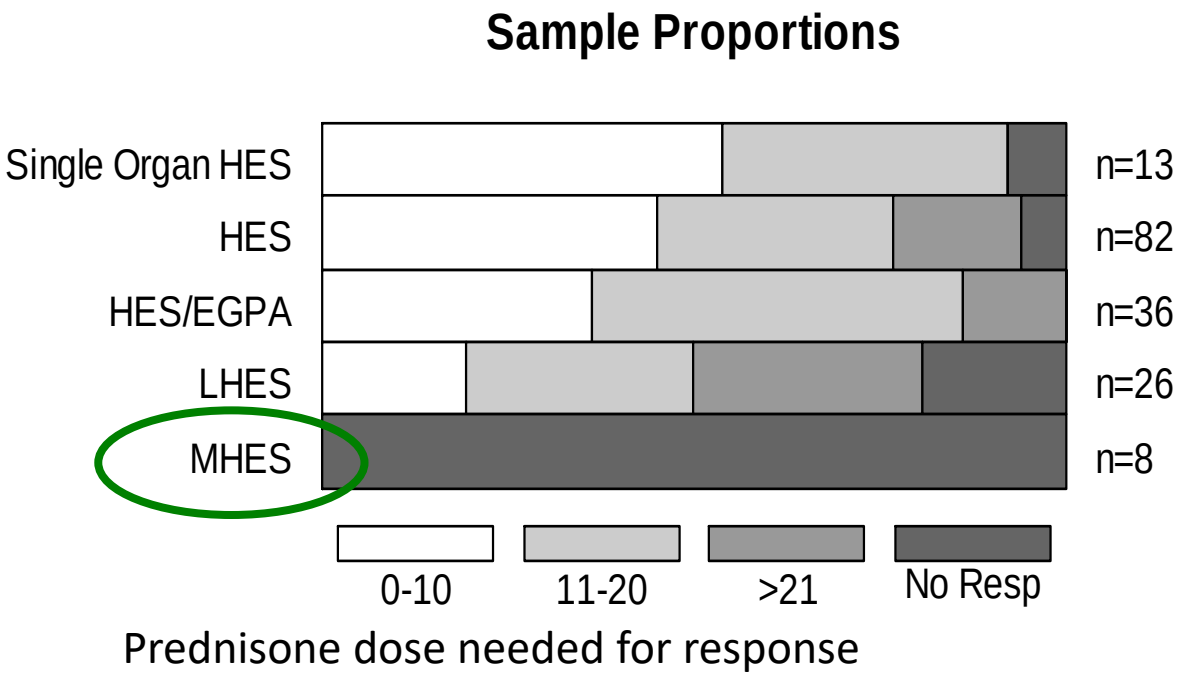
- NIH Evaluation (2018)
  - PE – splenomegaly (16 cm on CT-scan)
  - AEC 6300 despite 100 mg of prednisone
  - Tryptase 19.7
  - Repeat BM – atypical MC,
  - *FIP1L1-PDGFRA positive* detected by RT-PCR in blood and bone marrow
- Treated with imatinib and responded symptomatically, hematologically and histologically (GI tissue and bone marrow).

Diagnosis: Myeloid (F/P+) HES

Constantine G. et al JACI-P 2020

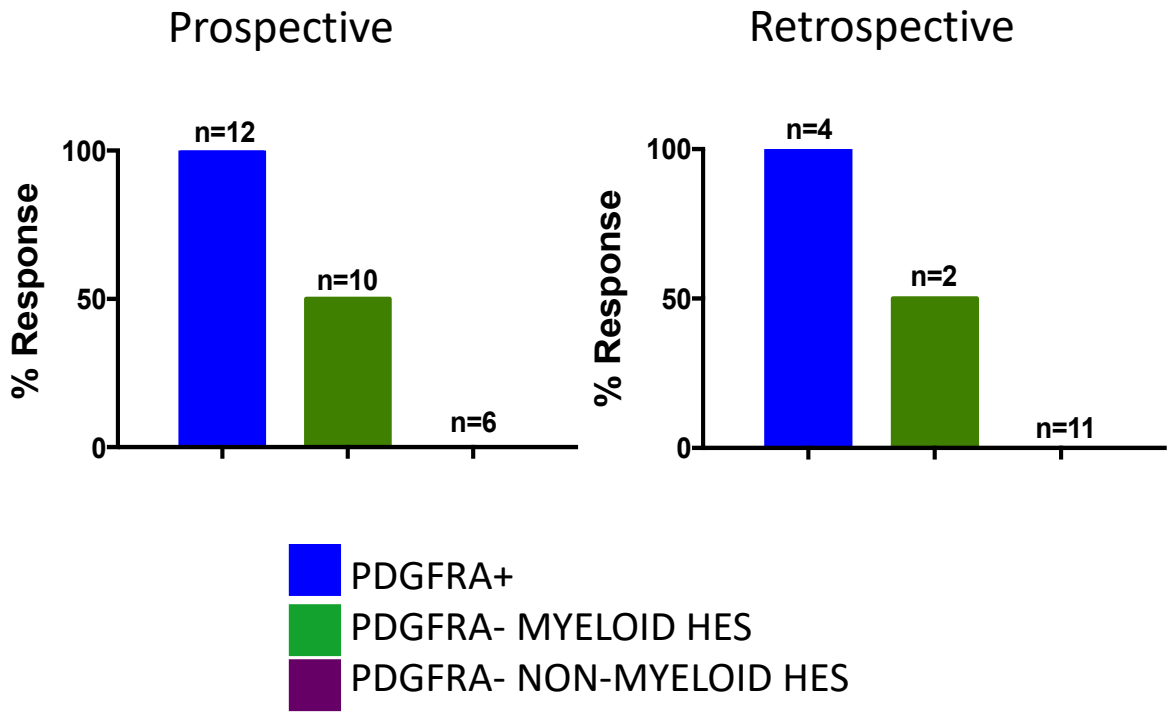
CLINICAL subtype predicts treatment responses

STEROIDS



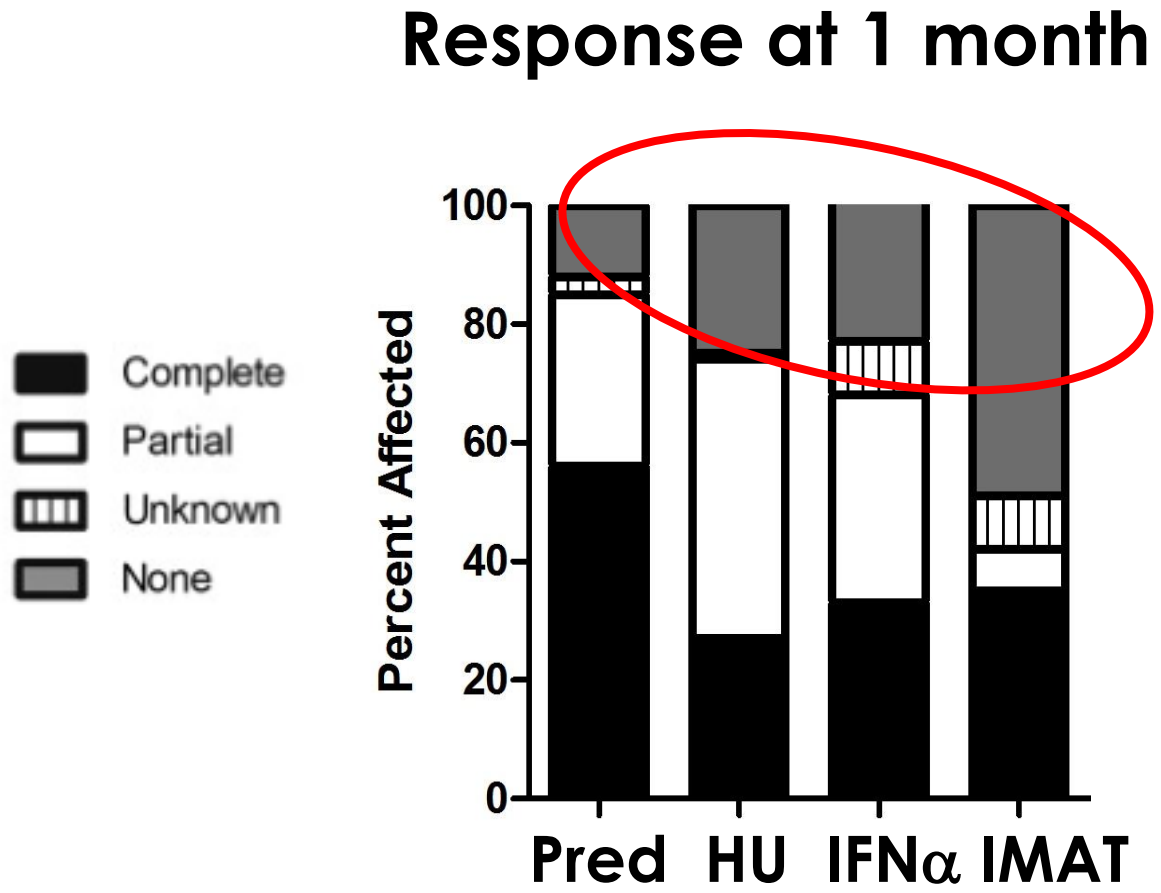
(Khoury et al. JACI in Practice 2018)

IMATINIB



(Khoury et al. Allergy 2016)

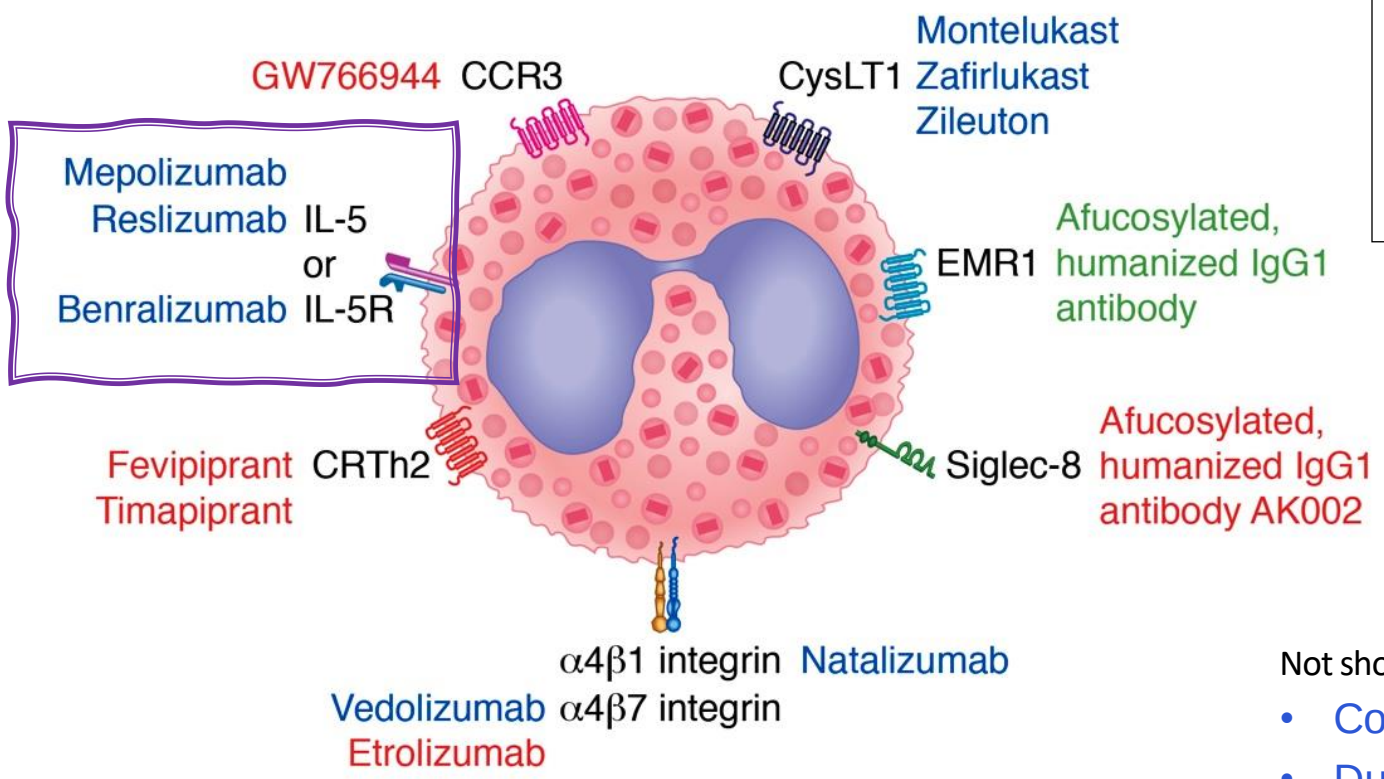
High rates of conventional drug discontinuation for HES treatment



Pred – Prednisone
HU – hydroxyurea
IFNα – interferon – α
IMAT - imatinib

(Ogbogu et al 2009 JACI)

Eosinophil-selective therapeutic targets in trials



Status:
Preclinical
In trials
Approved

Not shown:

- Corticosteroids
- Dupilumab (anti-IL-4Rα)
- Dexpramipexole

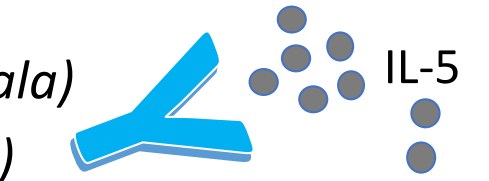
Dispenza and Bochner, Curr Hematol Malig Rep 2018; modified from Wechsler et al. J Allergy Clin Immunol 130:563, 2012

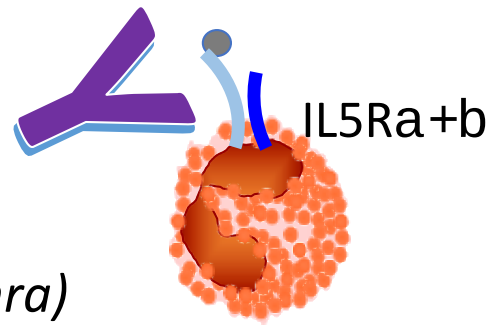
Use of Eosinophil Targeted Therapies in HES

Anti-IL-5 (Cytokine)

Mepolizumab *(Nucala)*

Reslizumab *(Cinqair)*





Anti-IL-5R (Receptor)

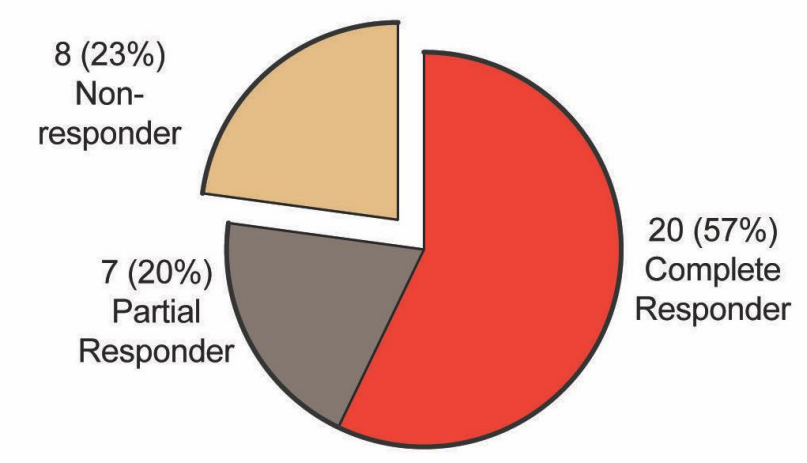
Benralizumab *(Fasenra)*

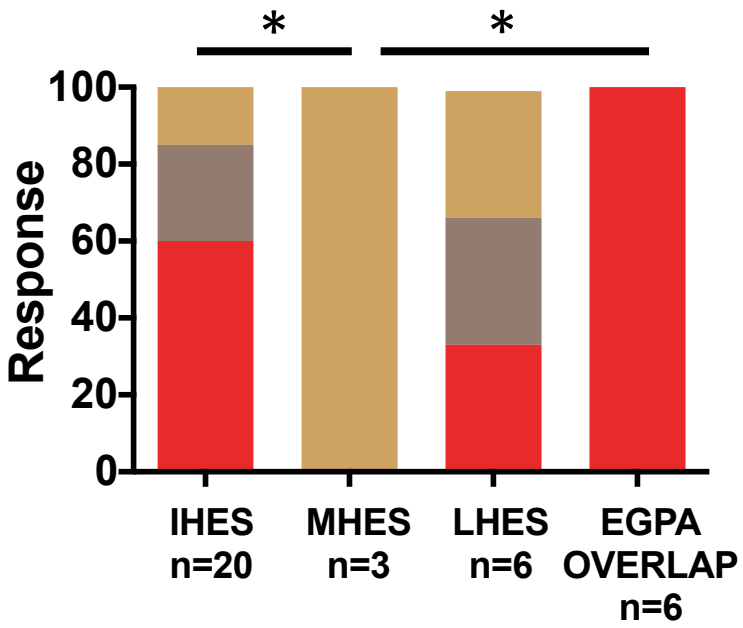
Eosinophil

Retrospective

Long-term clinical outcomes of high-dose mepolizumab for refractory HES

High-dose MEPO treatment is effective for severe, treatment-refractory HES





Non-Responders
Partial
Complete

HES clinical subtype matters

Kuang FL et al 2018, JACI In Practice

No significant differences in malignancy and mortality with MEPO treatment (EOS reduction)

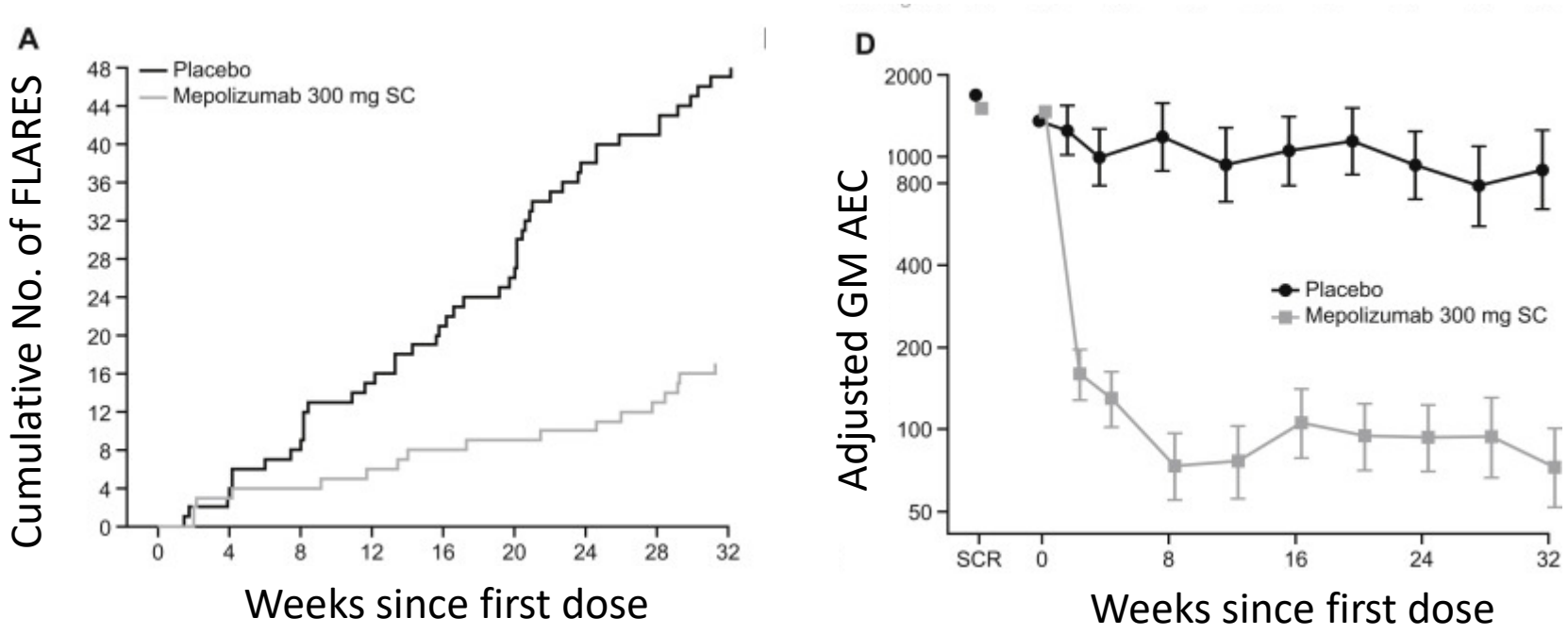
	CONTROL HES (n=55)	MEPO HES (n=23)
Median Follow-up in years (range)	7.3 (0.003-17.4)	8.5 (0.7 – 11)

…and no parasitic infection.

Kuang FL et al 2018, JACI In Practice

Ph3 Monthly MEPO 300 mg for HES reduces flares and decreases blood eosinophils

Note: enrolled only steroid sensitive HES patients; PDGFRA-negative



Flare: increase in symptoms or AEC requiring therapy escalation

FDA approved at 300 mg SC q 4 weeks in November 2020

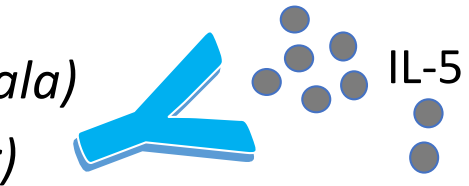
Roufosse F et al JACI 2020

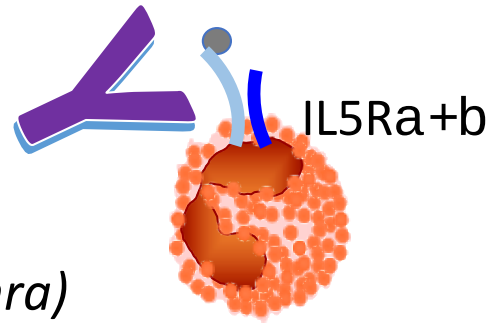
Use of anti-IL-5/IL-5R therapies in HES

<u>Anti-IL-5 (Cytokine)</u>

Mepolizumab *(Nucala)*

Reslizumab *(Cinqair)*





<u>Anti-IL-5R (Receptor)</u>

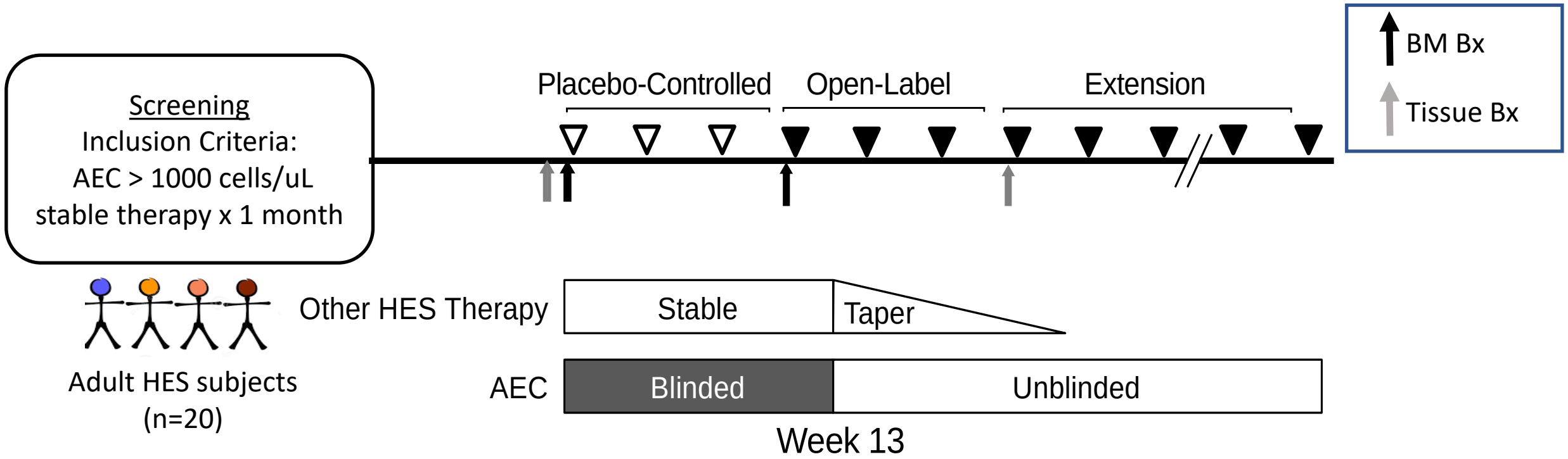
Benralizumab *(Fasenra)*

Eosinophil

<u>Prospective DBPCT</u>

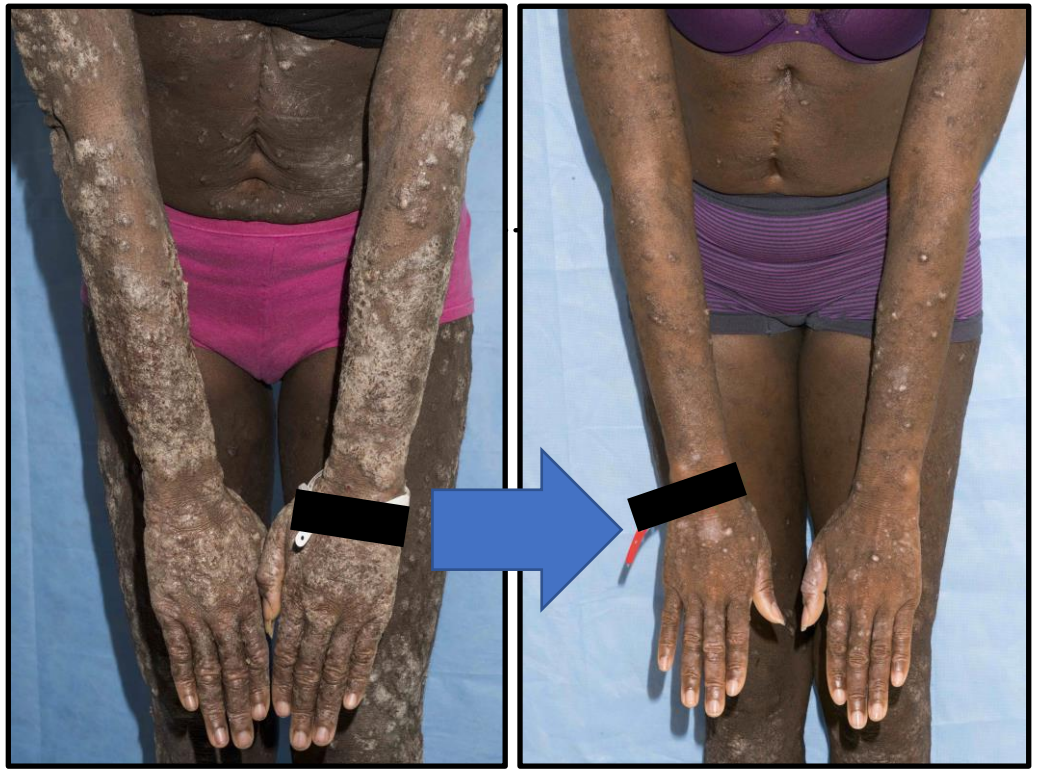
Benralizumab treatment for HES

Ph2 Benralizumab 30 mg SC for HES



Kuang FL et al NEJM 2019

BENRA depleted blood, tissue and bone marrow EOS in patients with HES

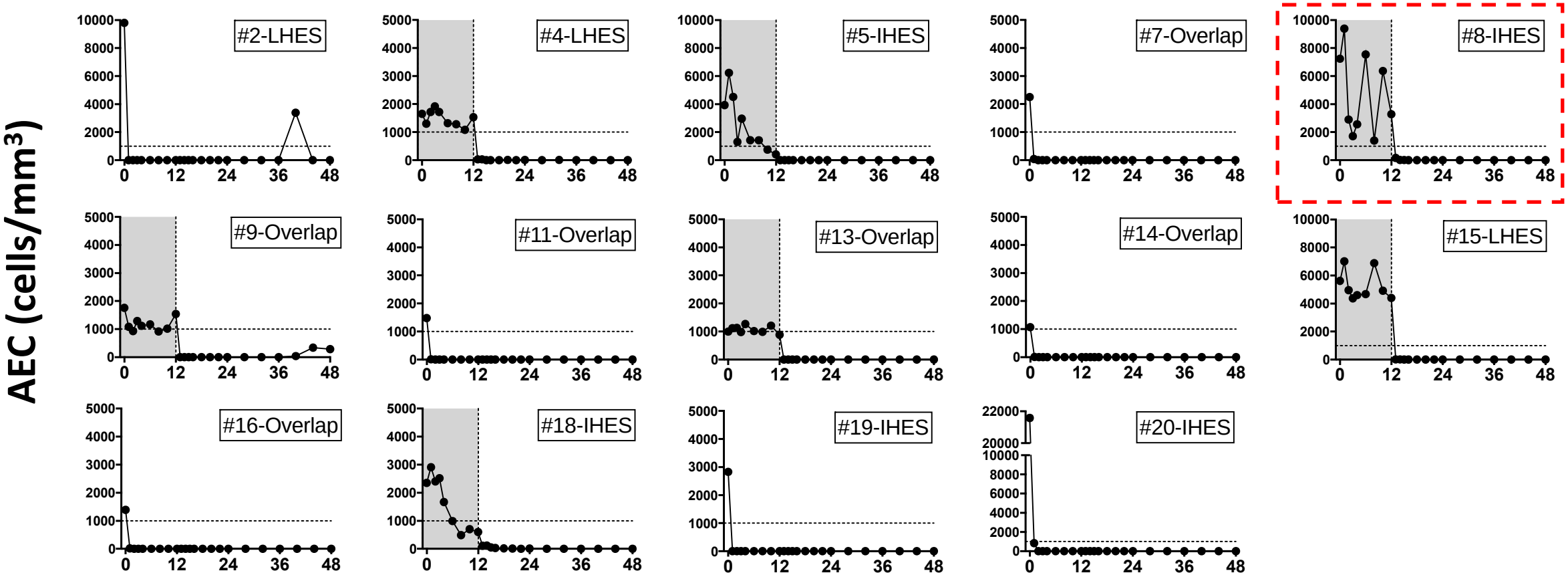


- Met Primary endpoint (p=0.02)
- Nearly all patients had **blood EOS = 0** in response to drug
- Tissue (GI) and bone marrow eosinophils were also depleted
- Improved symptoms and reduced use of background medications

Kuang FL et al NEJM 2019

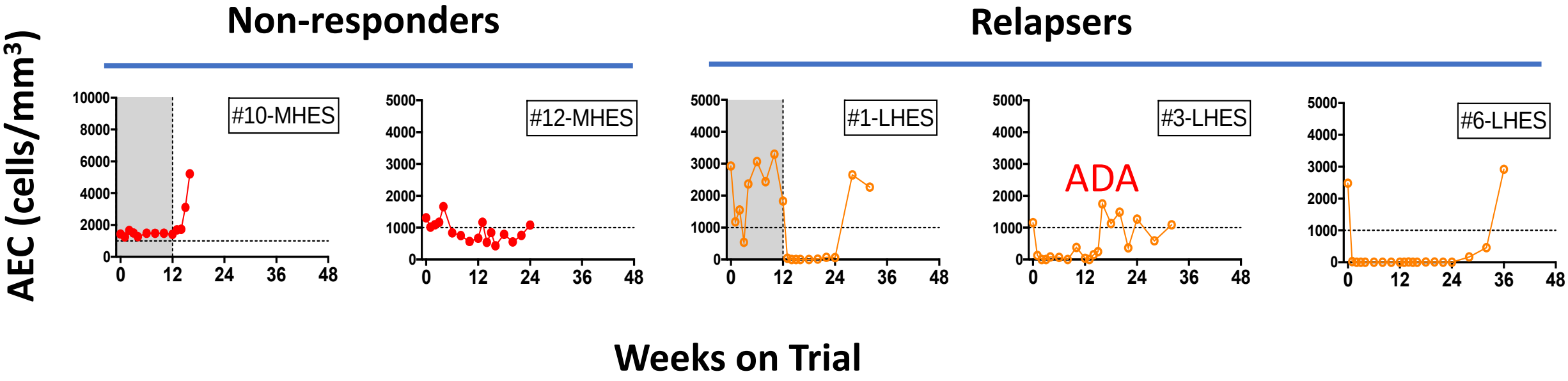
BENRA response rate in HES is 74% at week 48

Responders



Kuang FL et al NEJM 2019

BENRA response rate in HES is 74% at week 48

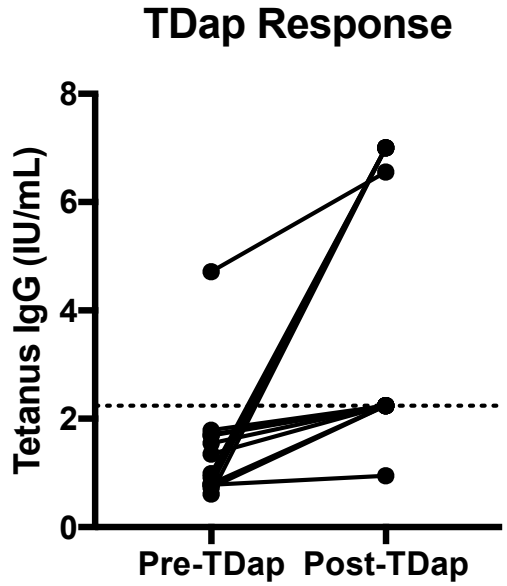


HES clinical subtype might matter
Development of anti-drug antibodies

Multinational, multi-site Phase 3 BENRA (anti-IL5R) for HES trial is ongoing

Clinical Observations after EOS Depletion with BENRA

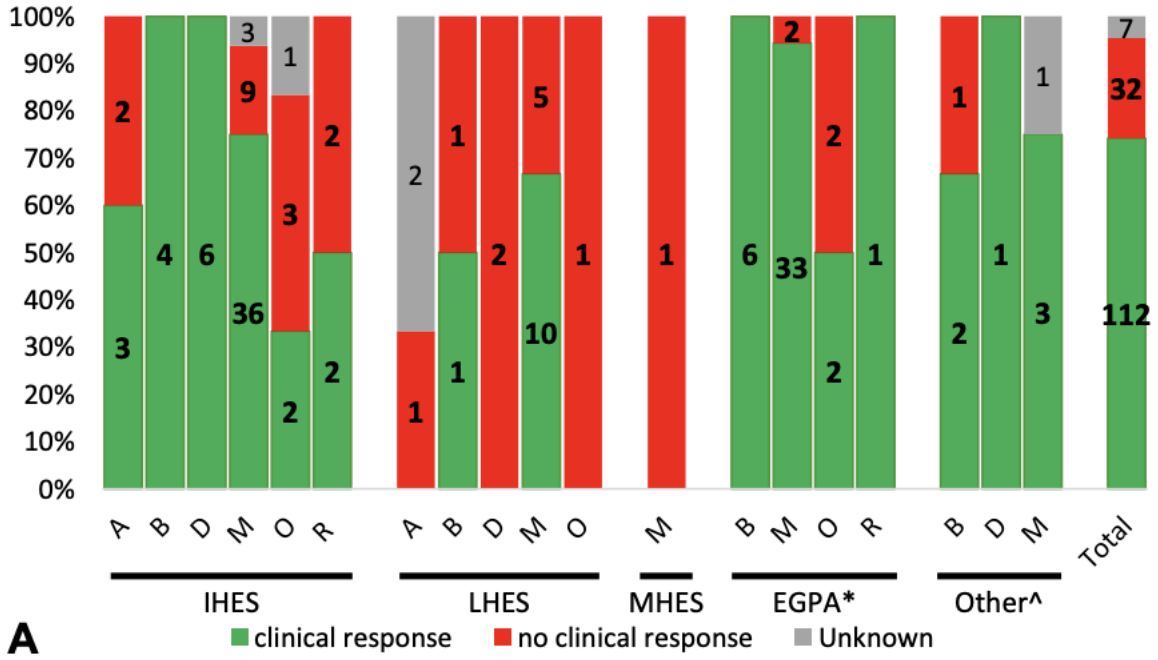
- No parasitic infections thus far
- Tetanus protein vaccine recall response intact
- No change in metabolic parameters (A1c and weight)
- Major abdominal surgery without report of healing problems (n=3)
- Successful pregnancy and healthy baby born without eosinophils (n=1)



Kuang FL manuscript in preparation

HES biologics treatment – multi-center experience

- International, retrospective study of real-world practice data on use of biologics in HES – outside of clinical trials

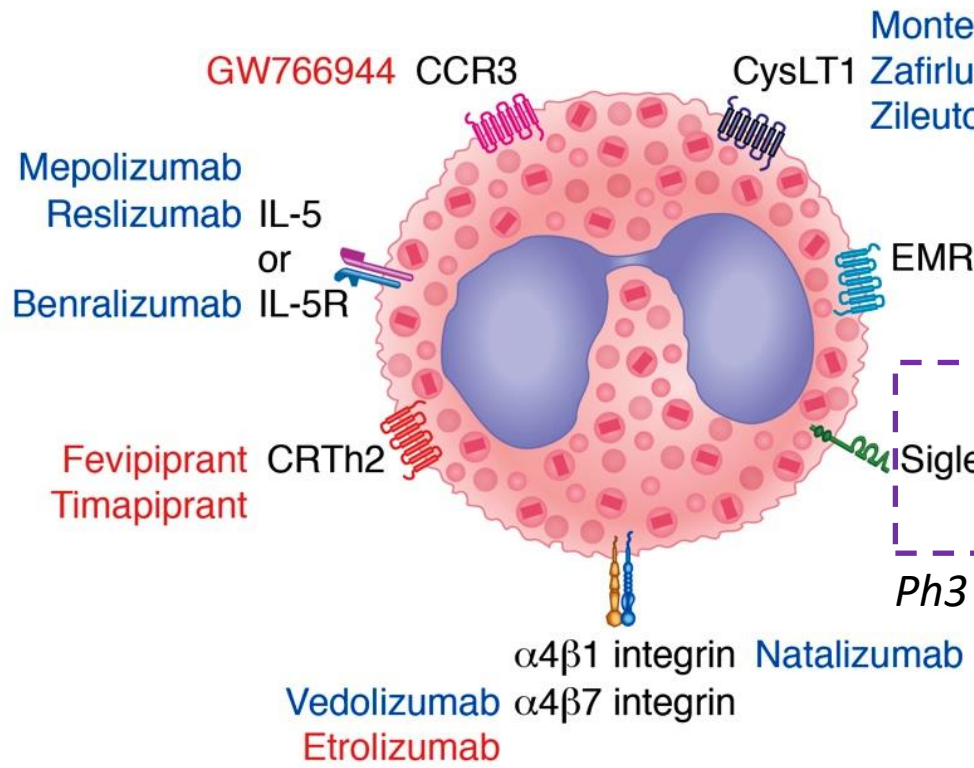


A – alemtezumab (CD52)
B – benralizumab (anti-IL5R)
D – dupilumab (anti-IL4R)
M – mepolizumab (anti-IL5)
O – omalizumab (anti-IgE)
R – reslizumab (anti-IL5)

HES clinical subtype matters

Chen MM et al JACI-P 2022

Eosinophil-selective therapeutic targets in trials



Status:
Preclinical
In trials
Approved

Ph3 for Eosinophilic Gastritis (EG)

Not shown:

- Corticosteroids
- Dupilumab (anti-IL-4Rα)

EoE and EG

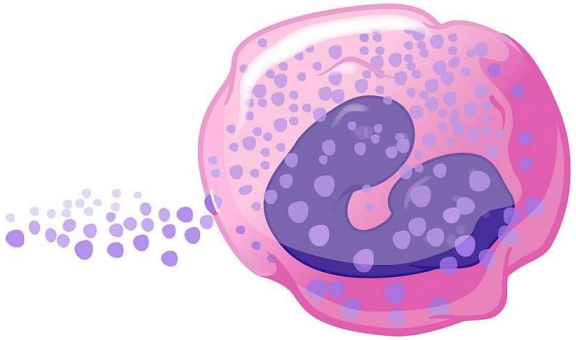
- Dexpramipexole

Ph2 in HES, now in asthma

Dispenza and Bochner, Curr Hematol Malig Rep 2018; modified from Wechsler et al. J Allergy Clin Immunol 130:563, 2012

Kuang FL and Bochner BS "Lessons learned from targeting eosinophils in human disease" Semin Immunopathol 2021 Jun;43(3):459-475

Summary



- HES's are a heterogeneous group of diseases
- Eosinophil reduction (MEPO) and depletion (BENRA) are effective and safe therapies in HES for a variety of clinical subtypes
- HES Clinical subtype matters for response to corticosteroid, imatinib and possibly anti-IL5 and IL-5R therapy
- No signal for vaccine response/metabolic/wound healing/host defense issues seen in eosinophil deficient people seen thus far
- These and other eosinophil-targeted therapies are teaching us about the contribution of eosinophils to specific diseases.

In HES, when to reconsider diagnosis…
… when to refer

- If you can't get access to some of the specialized testing (flow cytometry) and the suspicion is high for myeloid or lymphoid HES

  MD Anderson does RT-PCR for *FIP1L1-PDGFRA*

- If patient is having odd responses to corticosteroids or mepolizumab

- Referral to NIAID/NIH – Dr. Amy Klion Study ID: 94-I-0079
  - Patient needs to be willing to travel to Maryland, be part of research protocol
  - Requires local physician to provide referral/records and continued care

Division of Allergy Immunology

Kuang Lab
Richard Kasjanski
Krishan Chhiba
Mighty Sandhyapagu

Allergy Clinical Faculty,
Fellows, and Clinic Staff

Mentoring Team
Bruce Bochner
Cecilia Berin
Seema Aceves
Hirohito Kita

Ikuo Hirano
Nimi Gonsalves

Thank you!

K23AI171085

Laboratory of Parasitic Diseases
Human Eosinophil Section
Amy Klion
Paneez Khoury
Michelle Makiya
Brent Piligian
Clinical Parasitology Section

Laboratory of Allergic Disease

Sheila Kumar (NIDDK)
Bryan Curtin (NIDDK)
Astin Powers (Pathology)
Martha Quezado (Pathology)
Stefania Pittaluga (Pathology)

NIAID A/I Fellowship Program