Update on hypereosinophilic syndrome & Churg-Strauss syndrome

Dept. Allergy and Clinical Immunology,
Ajou University School of Medicine, Suwon, Korea

Yoo Seob Shin

Table of contents

Hypereosinophilic syndrome (HES)

History of HES

- Chusid's original definition at 1975
  - ✓ Blood eosinophilia > 1500/µL longer than 6 months
  - ✓ **And** no evidence of secondary causes
  - ✓ **And** signs and symptoms of organ involvement/dysfunction
- Revised definition at 2010
  - ✓ Blood eosinophilia > 1500/µL on at least two occasions
  - ✓ **Or** evidence of tissue eosinophilia associated with symptoms
  - ✓ **And** exclusion of secondary causes of eosinophilia

Chusid et al. Medicine (Baltimore) 1975;54:1-27
Simon et al et al. J Allergy Clin Immunol 2010;126:45-9

Classification of HES according to HES working group

1. Myeloproliferative HES
   - Primary disorder of the myeloid lineage
2. Lymphocytic variant HES
   - Clonal lymphocytes secreting Eos promoting cytokines
3. Overlap HES
   - Restricted to specific organ (ex. EGID, Eos pneumonitis)
4. Familial HES
   - Rare inherited form of HES

Klion et al. J Allergy Clin Immunol 2006;117:1292-302

Diagnostic work-up of consensus task force

- Laboratory studies
  - CBC with differential count / PB smear
  - Chemistry
  - for myeloproliferative HES
    : Vitamin B12, tryptase, PDGFR analysis (peripheral and BM)
  - for lymphocytic HES
    : flow cytometry for T cell phenotyping

- HES can involve every organ system
  - Heart: EKG, Echocardiogram…
  - GI organ: EGD, Colono, abdominal CT
  - Lung: PFT, chest CT
  - BM biopsy: rule out neoplastic disease
  - Tissue biopsy: tissue eosinophilia

Groh et al. Eur J Intern Med 2015;26:545-53

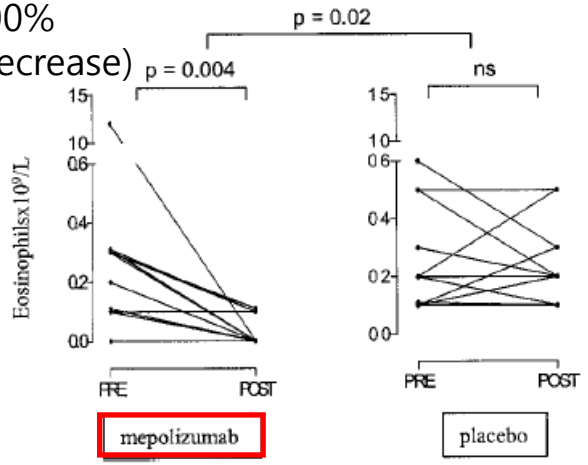
Absolute eosinophil count (AEC) as a biomarker of HES

- Inexpensive and accessible method
- Pro - association between elevated AEC (>100,000/mL) and poor prognosis
  - poor prognosis of myeloid HES which have higher AEC
- Con - relationship between AEC and tissue damage is not consistent
- Eosinophils are basically **tissue resident cells**
  - Half life in blood is about 18 hour
  - Survive in tissue for 8-12 days

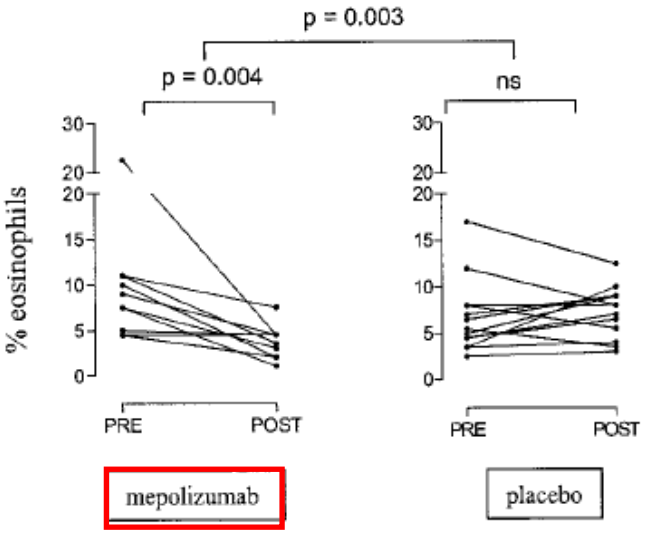
Fausi et al. Ann Intern Med 1982;182:78-92
Klion et al. Blood 2003;101:4660-6

Blood vs. Tissue eosinophilia

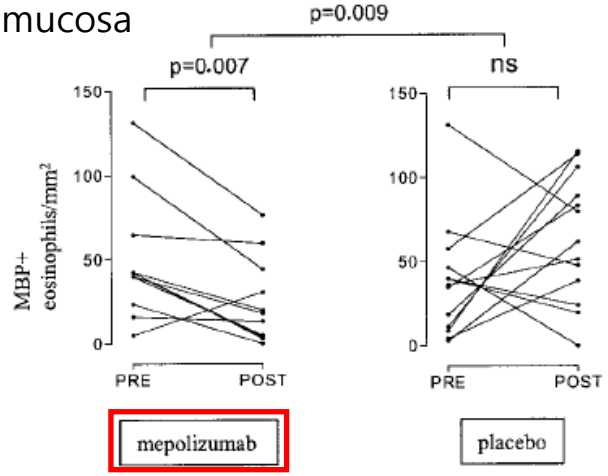
Blood - 100%
(median decrease)



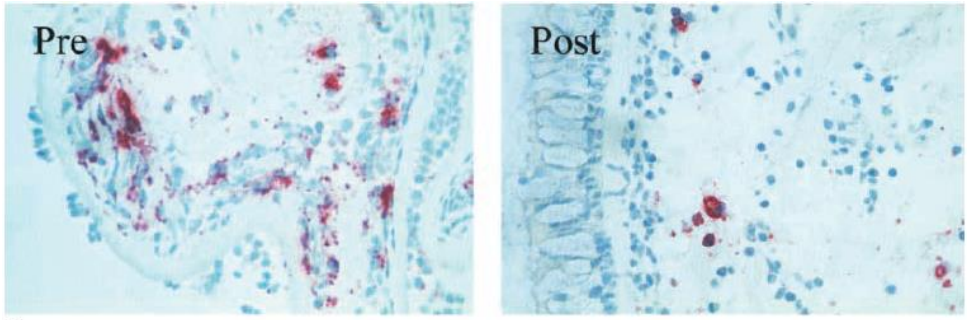
Bone marrow
- 52%



Bronchial mucosa
- 55%



Major basic protein (MBP) staining

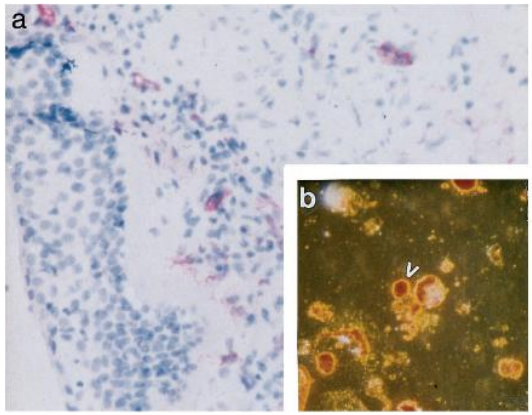


→ **restricted access or other pathwa**

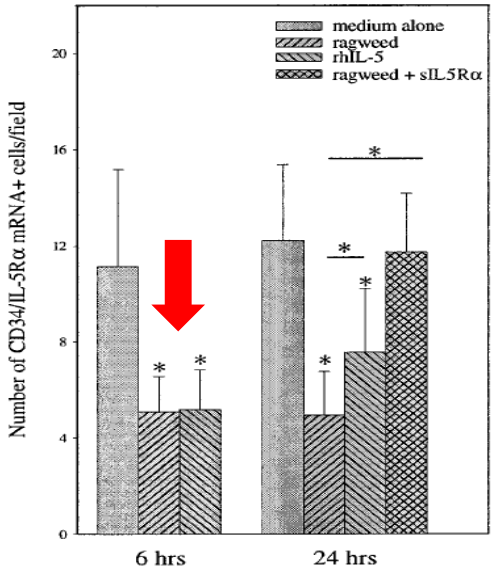
Flood-page et al. Am J Respir Crit Care Med. 2003;167(2):199-204

Another pathway of tissue eosinophilia

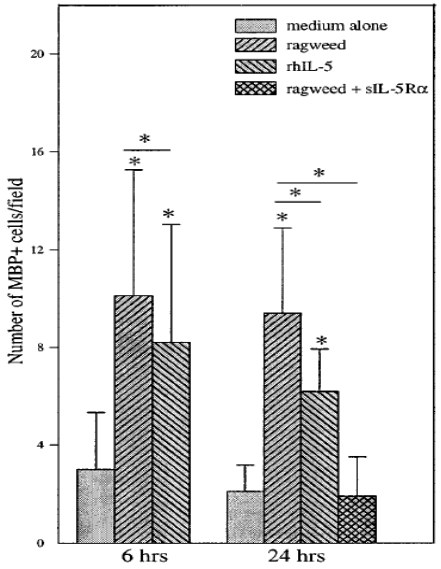
- Another cytokines for eosinophil (IL-3, GM-CSF, CCR3…)
- Localized maturation of eosinophil
  - in situ differentiation, local eosinophilopoiesis



CD34+ progenitor cells
in nasal mucosa



CD34+ cells were decreased
after allergen stimulation



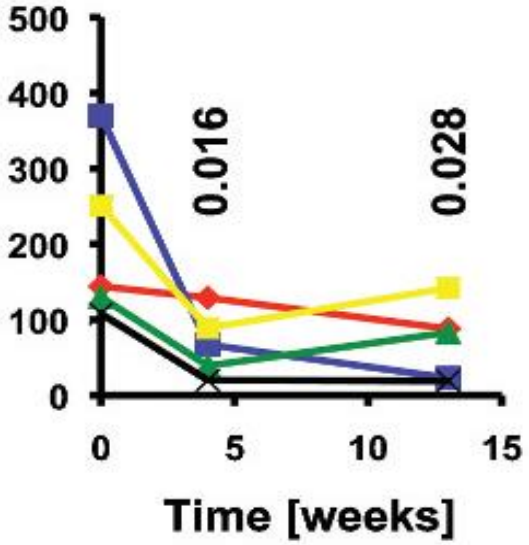
MBP+ cells were increased
after allergen stimulation

Cameron et al. J Immunol 2000;164:1538-1545

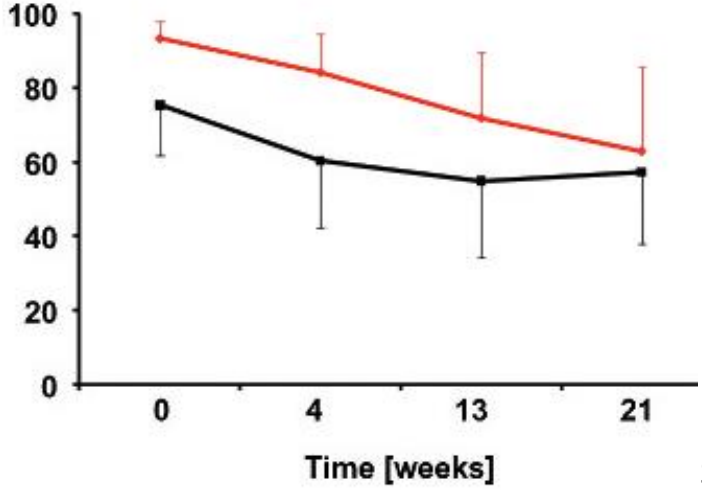
Tissue eosinophilia as a biomarker of HES

- Specific indicator
  but difficulty in sampling and patchy nature of infiltration
- Pro - The suppression of tissue Eos counts has been associated with **improved long-term prognosis** of EoE
- Con - tissue eosinophilia ≠ symptom improvement

<Tissue Eos>



<Dysphagia Symptom>



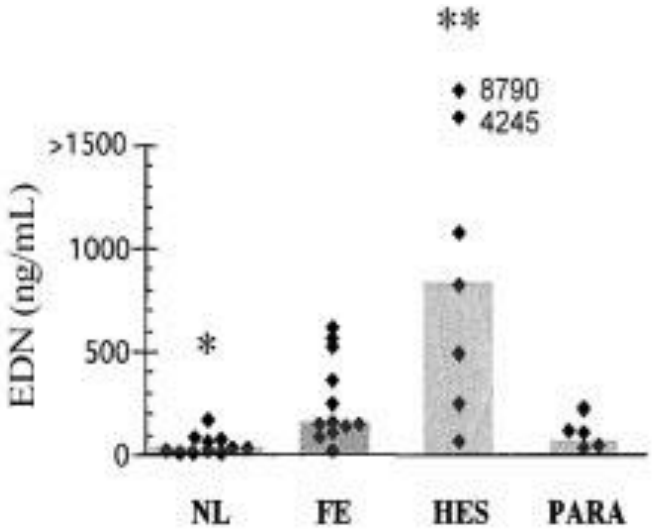
Red line – mepolizumab
Black line – placebo

Straumann et al. Gut 2010;59:21–30
Greuter et al. Gastroenterology 2007;133:1342-63

Eosinophil granule proteins as a biomarker of HES

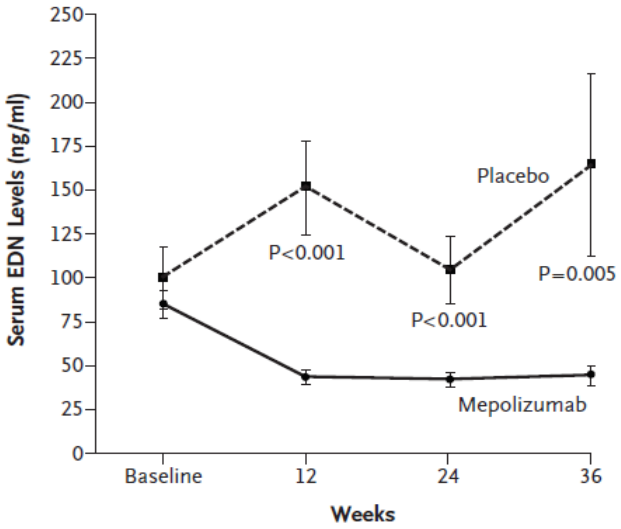
- Attractive candidate biomarker (eosinophilic activation)
  - MBP, EPO, ECP and EDN

<Between disease activities>



FE: familial eosinophilia
PARA: parasite infection

<Follow up after treatment>



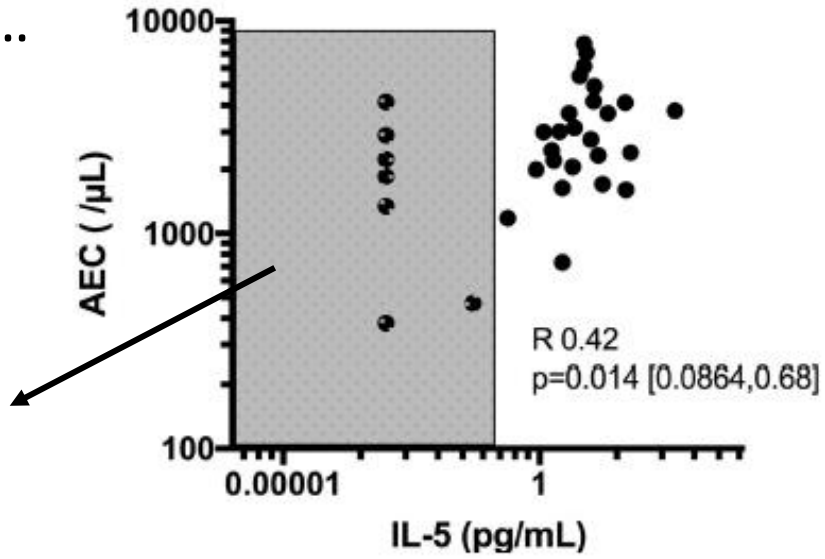
- Disadvantage – **false positive results** due to eosinophil lysis

Klion et al. Blood. 2004;103:4050-4055
Rothenberg et al. N Engl J Med 2008;358:1215-28

Other biomarkers of HES

- Eosinophil surface marker
  - IL-5Rα, CD69, CD44…
- Serum cytokines, chemokines and soluble receptors
  - **IL-5**
  - IL-25, CCL17, TARC, eotaxin-3…

Undetectable serum IL-5 in some patients with significant eosinophilia of untreated HES



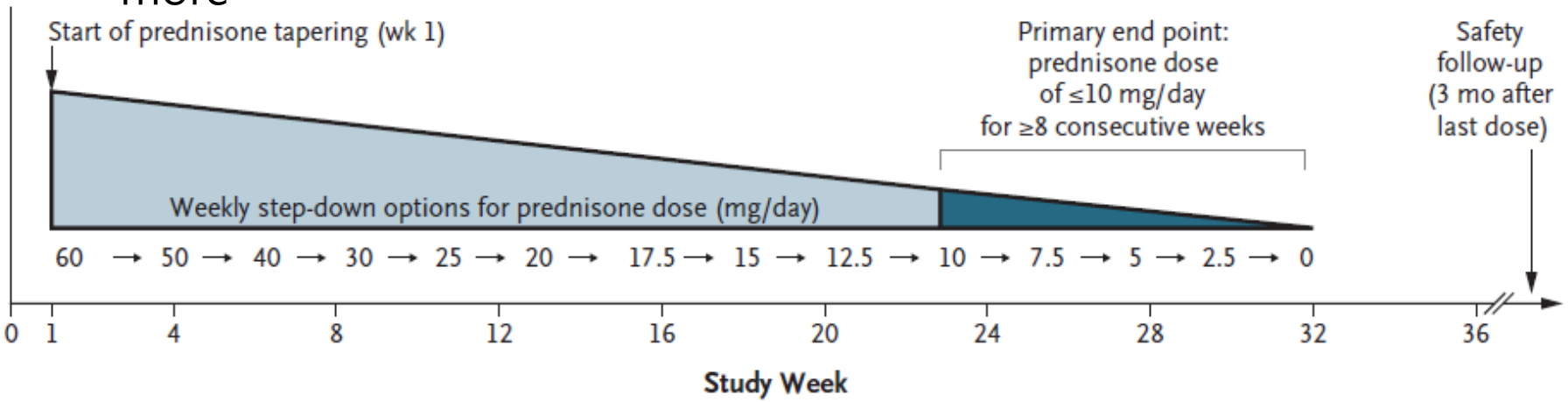
Wilson et al. J Allergy Clin Immunol 2011;128:1086–92

Treatment of HES

- Corticosteroid
- Cytotoxic agent
  - hydroxyurea, vincristine, MTX, cyclophosphamide…
- Immunomodulatory agent
  - IFN-α, cyclosporine…
- Imatinib mesylate
  - FIP1L1/PDGFRA mutation positive
- **Monoclonal antibody**
  - Mepolizumab, Reslizumab, Benralizumab

Effects of anti IL-5 antibody in HES

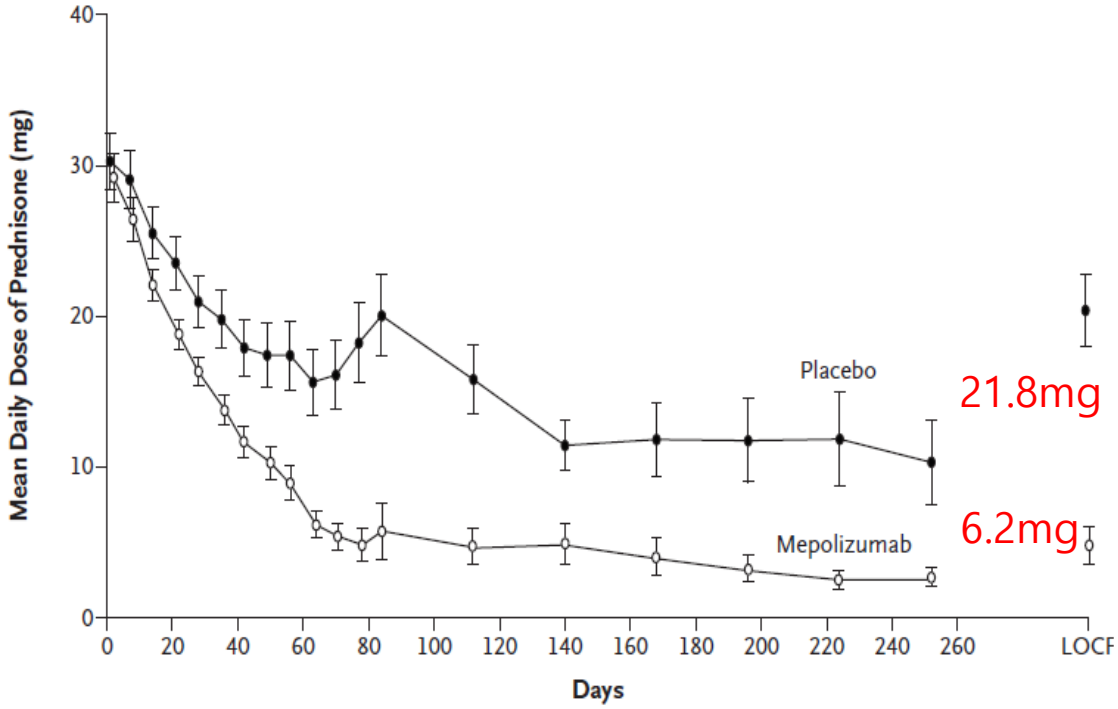
- Randomized, double-blind, placebo-controlled trial (36 weeks)
  - 26 centers in 8 countries
  - PDGFR gene (-) + daily requirement 20~60mg of prednisone
- Mepolizumab group (n=43) 750mg IV every 4 weeks + steroid Tx.
- Placebo group (n=42) placebo + steroid Tx.
- Primary end points
  - Reduction of prednisone dose to ≤10 mg /day for 8 week or more

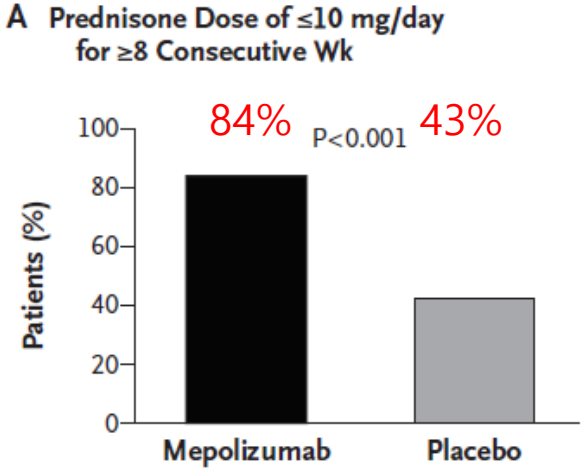


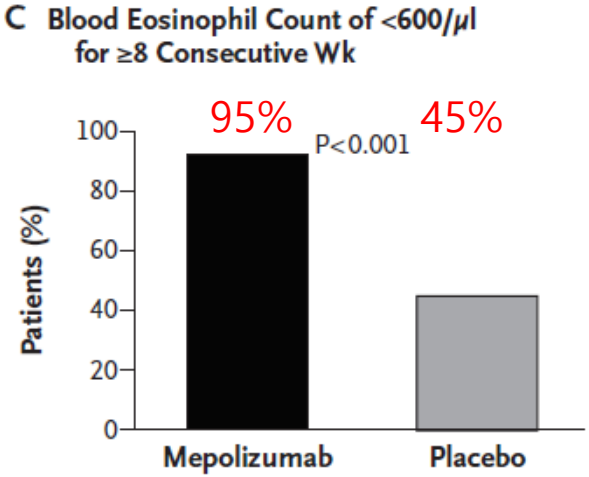
Rothenberg et al. N Engl J Med 2008;358:1215-28.

Effects of anti IL-5 antibody in HES

<Mean steroid dose>



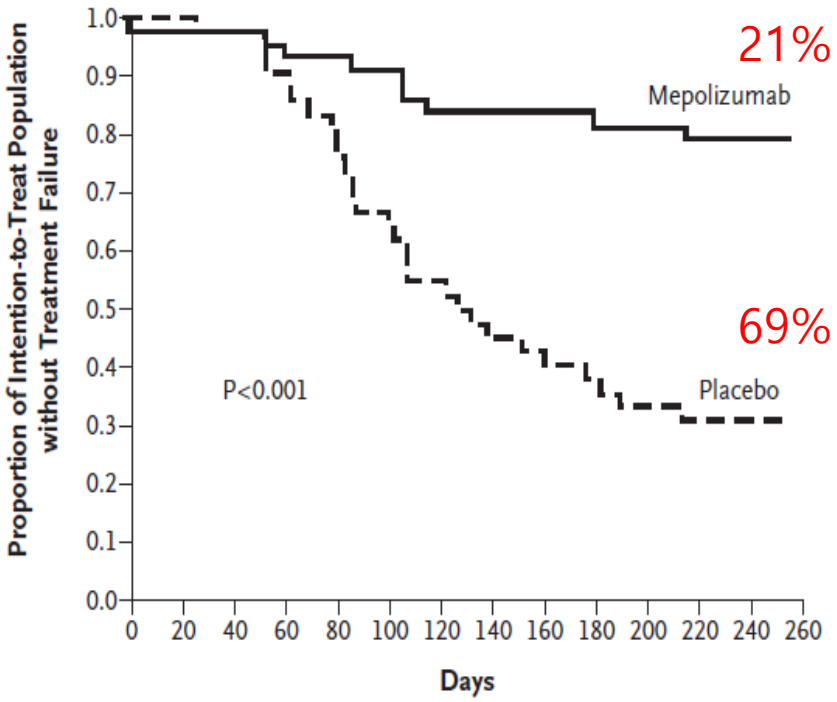




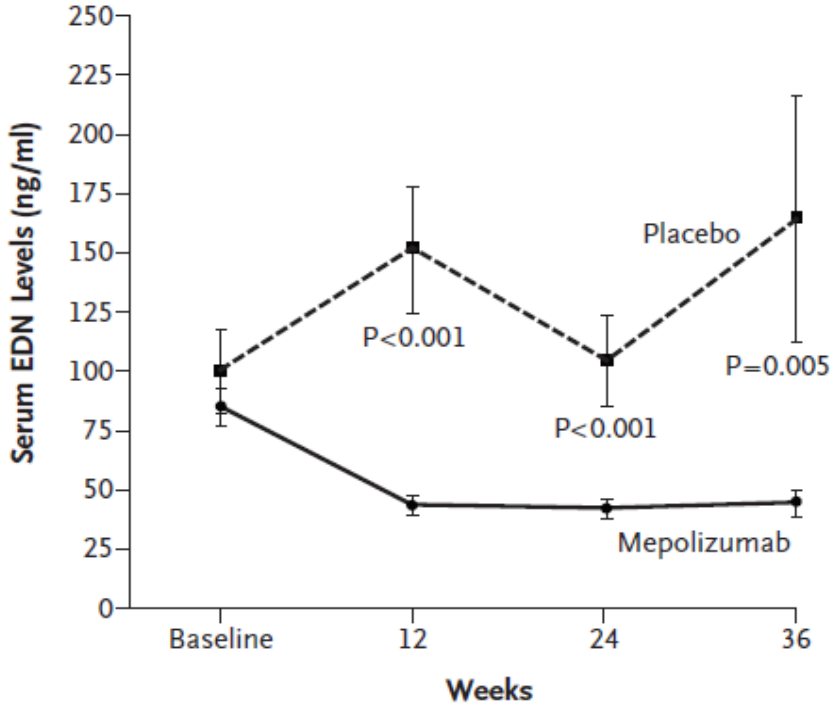
Rothenberg et al. N Engl J Med 2008;358:1215-28.

Effects of anti IL-5 antibody in HES

<Treatment failure>



<Serum EDN level>



→ Mepolizumab treatment enabled **significant reductions in corticosteroid dose**
with the **reduction of blood eosinophilia and its activation**.

Rothenberg et al. N Engl J Med 2008;358:1215-28.

Long-term safety issue of anti IL-5 in HES

- HES patients (n=78)
  - open label extension study of previous one
  - 1 to 66 mepolizumab infusions
  - mean infusions – 25 times
  - mepolizumab 750mg IV
  - **mean exposure duration 251 weeks** (4~302 weeks)

- Study purposes
  - the frequency of adverse events (AEs)
  - Optimal dosing frequency
  - corticosteroid-sparing effect of mepolizumab

Roufosse et al. J Allergy Clin Immunol 2013;131:461-7.

Long-term safety issue of anti IL-5 in HES

- Safety

TABLE II. AE rates per 12-month period adjusted for exposure

	Period (mo)					
	Control*	0-12	12-24	24-36	36-48	>48
Subject-years exposure	15.0	69.0	61.1	59.2	57.8	39.9
AEs						
No. of events	319	643	374	300	349	184
Event rate†	2127	931.9	612.1	506.8	603.8	461.1
SAEs						
No. of events	7	31	28	15	26	7
Event rate†	46.7	44.9	45.8	25.3	45.0	17.5

*Subjects who received placebo in the placebo-controlled, double-blind mepolizumab trial (MHE100185).
†Events per 100 subject-years exposure within period.

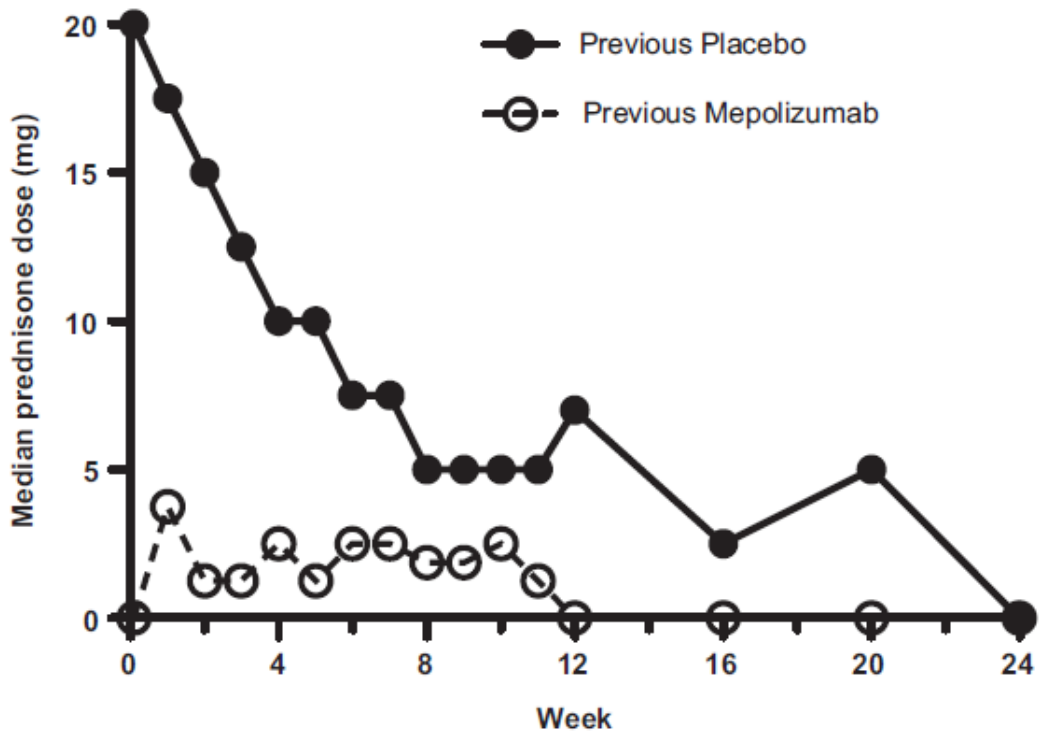
Cough, fatigue, headache, URI, & sinusitis were most common

Four mortalities
- T cell lymphoma
- adrenal insufficiency
- atrial fibrillation
- sepsis, cardiac failure

Roufosse et al. J Allergy Clin Immunol 2013;131:461-7.

Long-term safety issue of anti IL-5 in HES

- Efficacy



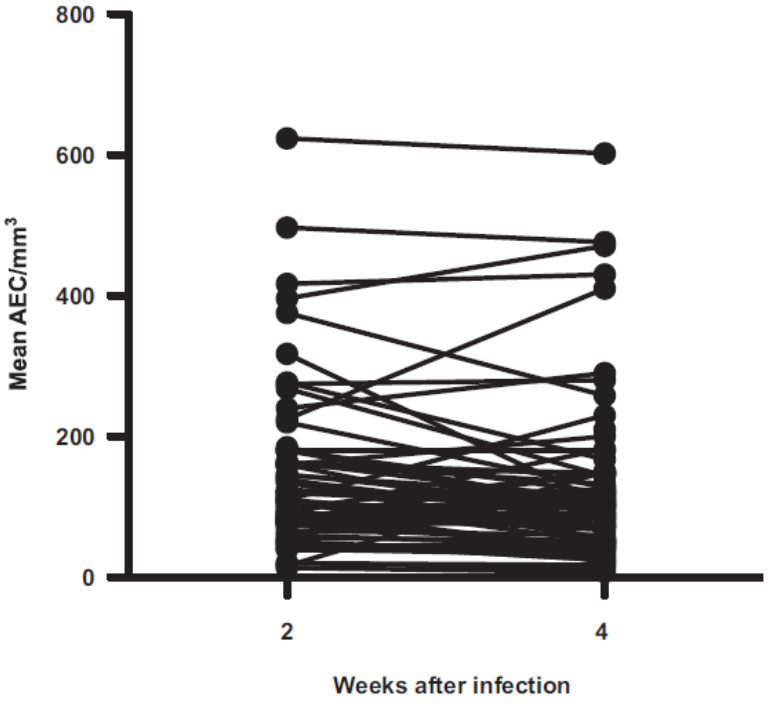
<Mepolizumab group>

- The median average daily prednisone dose for 78 subjects over the course of the study was **1.8 mg**.
- Forty-eight of 78 subjects (**62%**) received **mepolizumab monotherapy for HES** for >12 consecutive weeks.

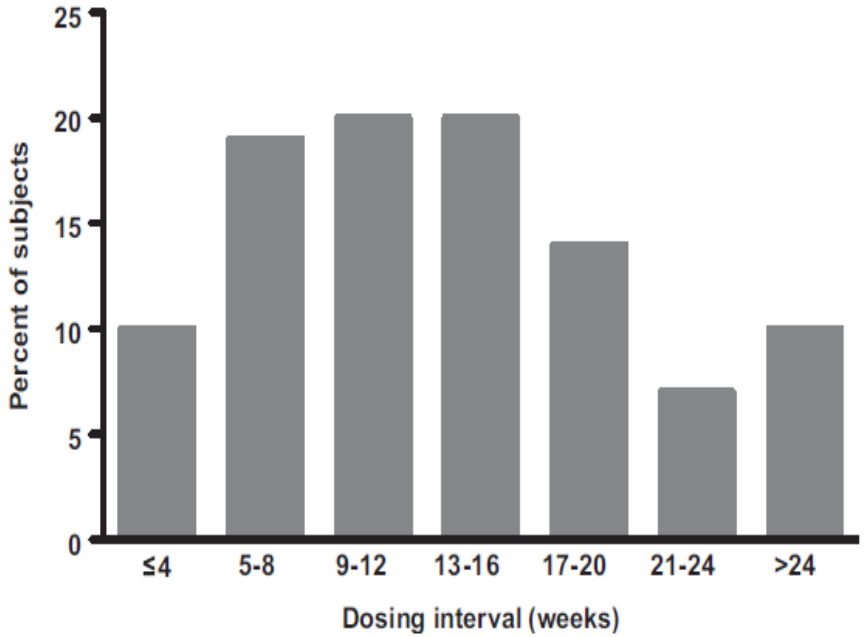
Roufosse et al. J Allergy Clin Immunol 2013;131:461-7.

Long-term safety issue of anti IL-5 in HES

- Eosinophilia



- Mepolizumab dosing interval

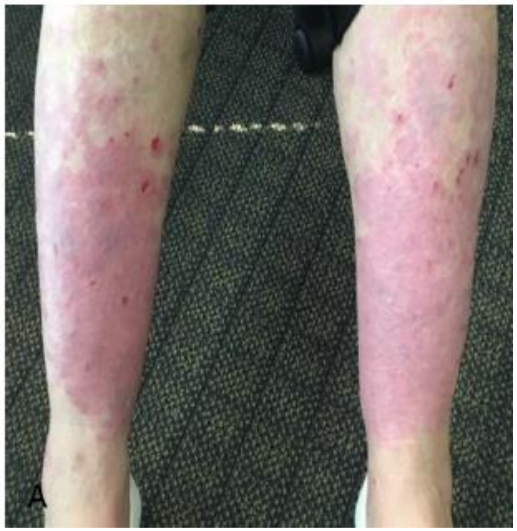


- Mean AEC remained below 500/mm3 in all but 1 subject
- The median dosing interval for all subjects was **12.8 weeks**

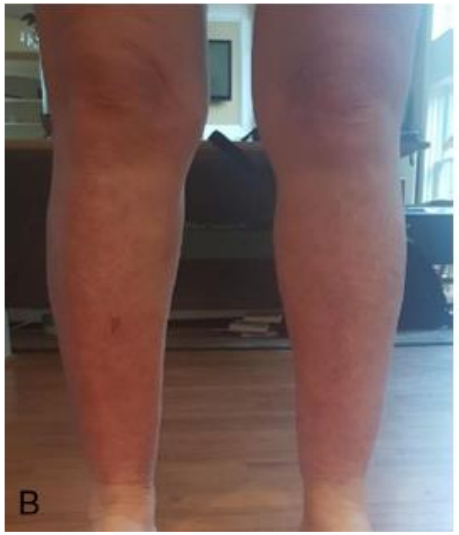
Roufosse et al. J Allergy Clin Immunol 2013;131:461-7.

Effect of reslizumab in HES

- 55 year old, female patient
- Eczematous skin lesion with severe pruritus on both legs
  Bx. spongiotic dermatitis with eosinophil infiltration
- Nausea, vomiting, diarrhea
  Bx. eosinophilic infiltration of esophagus (50/HPF)
- Blood eosinophil – 1200 cells/uL on prednisone 10~20mg/day



Reslizumab
3mg/kg/month



7 month
later

Kuruvilla et al. Ann Allergy Asthma Immunol. 2018;120:670-1.

Eosinophilic granulomatous polyangiitis (EGPA)

Definition of EGPA

- Small vessel vasculitis with asthma and eosinophilia
  - First described in 1951 by Jacob Churg and Lotte Strauss
  - Renamed based on the 2012 revised Chapel Hill Consensus Conference

- Heterogeneous disease between ANCA vasculitis and HES
  - subtypes based on ANCA status (37.6%) among 93 patients

	ANCA positive	ANCA negative	*P* value
Constitutional Symptom	85.7%	56.9%	0.006
Purpura	**25.7%**	6.9%	0.015
Lung involvement	34.3%	**60.3%**	0.019
Pulmonary hemorrhage	**20.0%**	0%	0.001
Heart involvement	5.7%	**22.4%**	0.042
Mononeuritis multiplex	**51.4%**	24.1%	0.013
Renal involvement	**51.4%**	12.1%	< 0.001

Sinico et al. Arthritis Rheum 2005;52:2926-35

Sputum ANCA in EGPA

- Serum ANCA (+) – vasculitis predominance
- Serum ANCA (-) – cardio-pulmonary manifestations

→ If ANCA is localized to the lungs ?

- 23 EPGA patients
  - 10 ANCA (+) EGPA
  - 13 ANCA (-) EGPA
- 19 severe asthma patients
- 13 healthy control

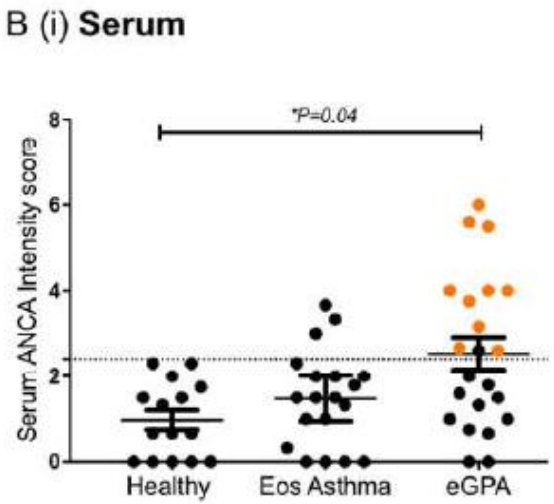
Matched **serum** and **sputum** sampling

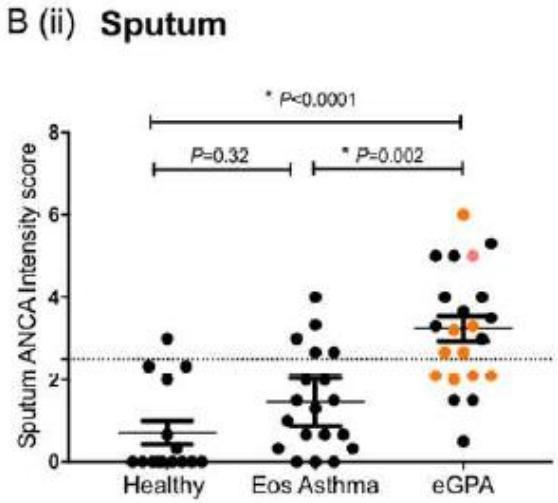
Mukherjee et al. Am J Respir Crit Care Med. 2018 Sep 4

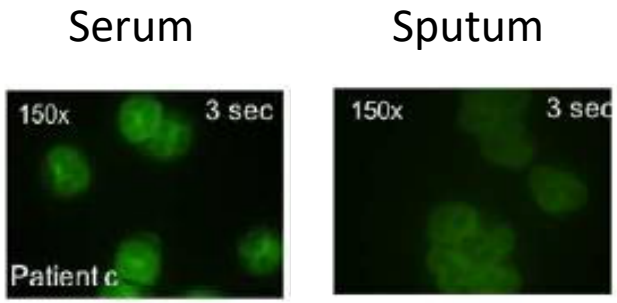
Sputum ANCA in EGPA

<ANCA positivity>

Parameter	Sputum + Serum +	Sputum + Serum -	Total
EGPA	7/10	**10/13**	17/23
Asthma	1/3	4/16	5/19
NC	0/12	1/12	1/13







Mukherjee et al. Am J Respir Crit Care Med. 2018 Sep 4

Diagnosis of EGPA

- Lanham diagnostic criteria (1984)
  - Asthma
  - Blood eosinophilia > 1500/mm^3 or >10% of WBC
  - Evidence of vasculitis involving 2 or more organ
- American College of Rheumatology criteria (1990)
  - Asthma
  - Neuropathy
  - Paranasal abnormality
  - Eosinophilia >10% of WBC
  - Pulmonary infiltration
  - Extravascular eosinophilia
- Revised Chapel Hill Consensus Conference (2012)

  - **Eosinophil-rich and necrotizing granulomatous inflammation** often involving the **respiratory tract**, and **necrotizing vasculitis** predominantly affecting small-to-medium vessels, and associated with **asthma and eosinophils**.

Five-Factor Score (FFS) of French Vasculitis Study Group

< 1996 version>

1. Proteinuria (>1 g/24 hours)
2. Renal insufficiency (creatinine >1.58 mg/dL)
3. Cardiac involvement
4. Severe gastrointestinal manifestations
5. CNS involvement

<5-year mortality>
- Score 0 ; 12%
- Score 2 or more ; 46%

< 2009 version>

1. Age >65 years
2. Cardiac insufficiency
3. Renal insufficiency (creatinine >1.70 mg/dL)
4. Gastrointestinal involvement
5. **Absence of ENT manifestations**

<5-year mortality>
- Score 0 ; 9%
- Score 2 or more ; 40%

Guillevin et al. Medicine (Baltimore) 1996;75:17-28.
Guillevin et al. Medicine (Baltimore) 2011;90:19-27.

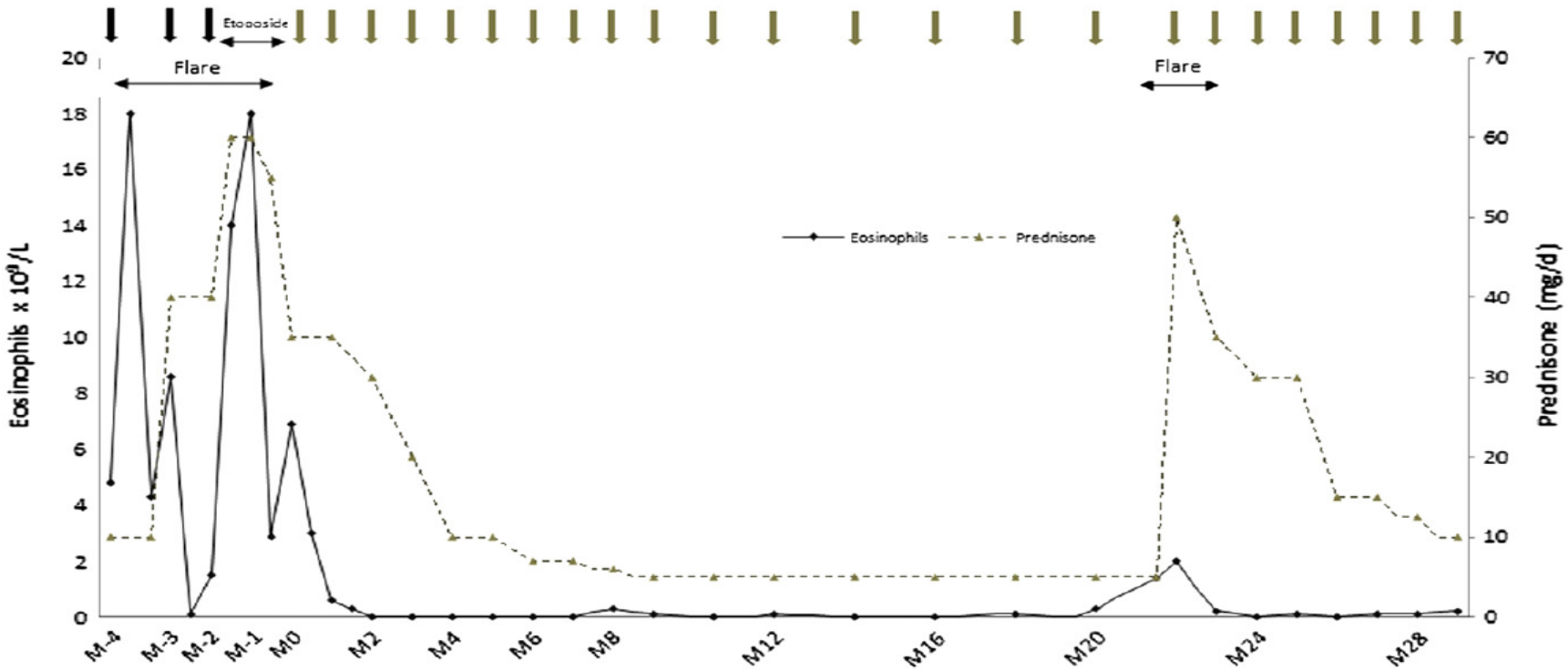
Treatment for EGPA

- Corticosteroid
- Cyclophosphamide
- Azathioprine
- Methotrexate
- Plasma exchange
- Rituximab
- IVIG
- Interferon-alpha
- **Anti-IL-5 monoclonal antibody**

Groh et al. Eur J Intern Med 2015;26:545-53

First report of anti IL-5 antibody in EGPA

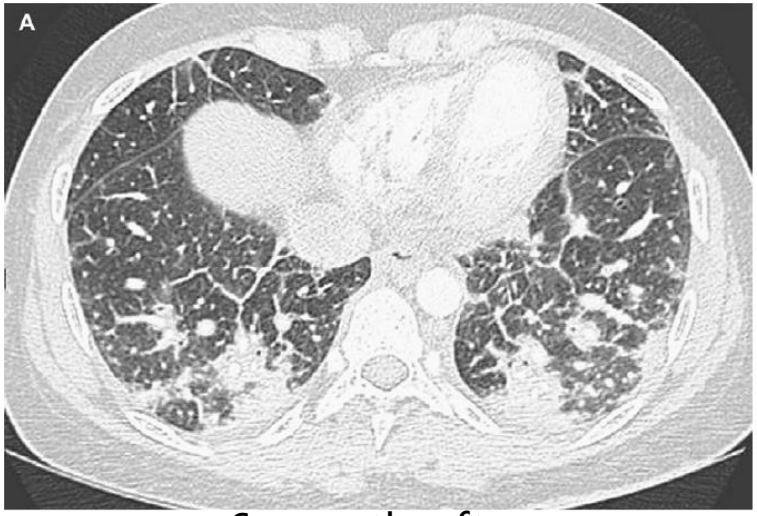
- F/28 (asthma, eosinophilia, interstitial pneumonia, myocarditis)
- Mepolizumab 750mg IV, monthly (3 times)



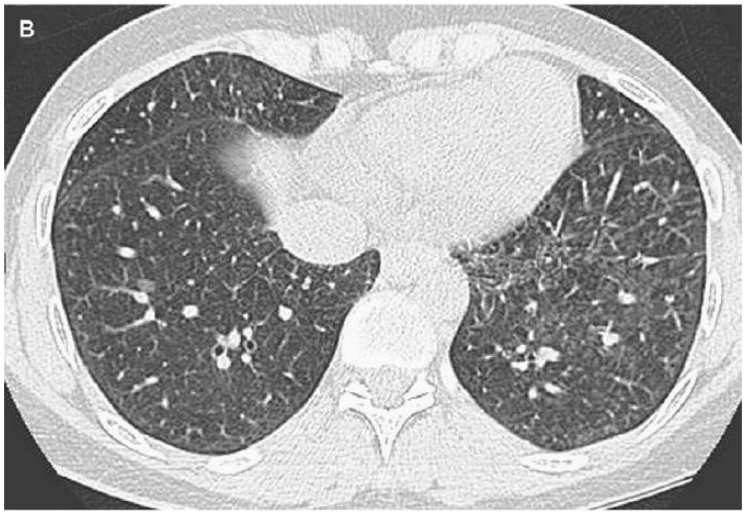
Kahn et al. J Allergy Clin Immunol 2010;125:267-70.

First report of anti IL-5 antibody in EGPA

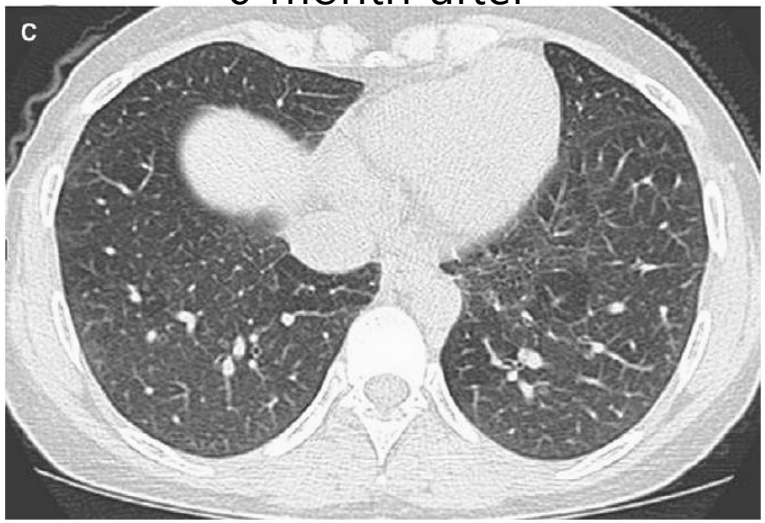
Before



1 month after



6 month after



- Blood as well as tissue eosinophilia ↓

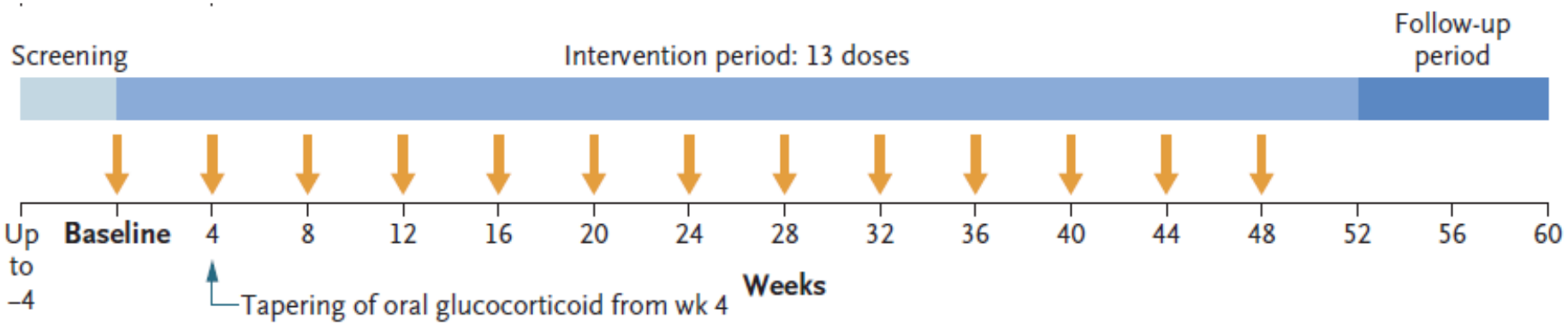
TABLE I. Evolution of serum IL-5 and ECP levels 2 months before and 2 months and 8 months after initiation (mo) of monthly pulses of mepolizumab

	M–2	M+2	M+8
IL-5 (pg/mL)	19.89	66.2	60.1
ECP (μg/L)	>200	27	12.3

Kahn et al. J Allergy Clin Immunol 2010;125:267-70.

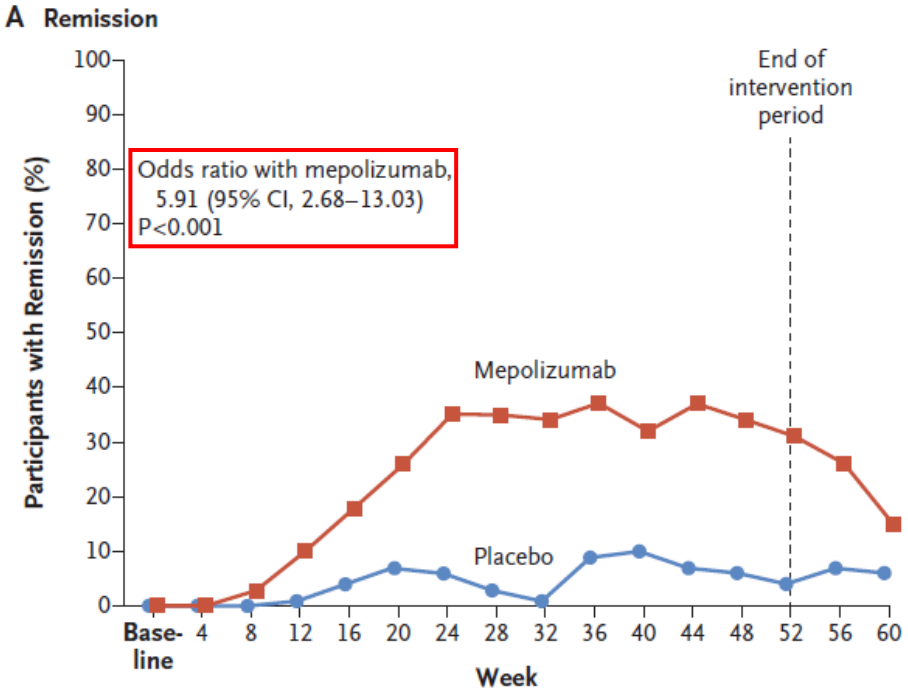
Phase 3 trial of mepolizumab in EGPA

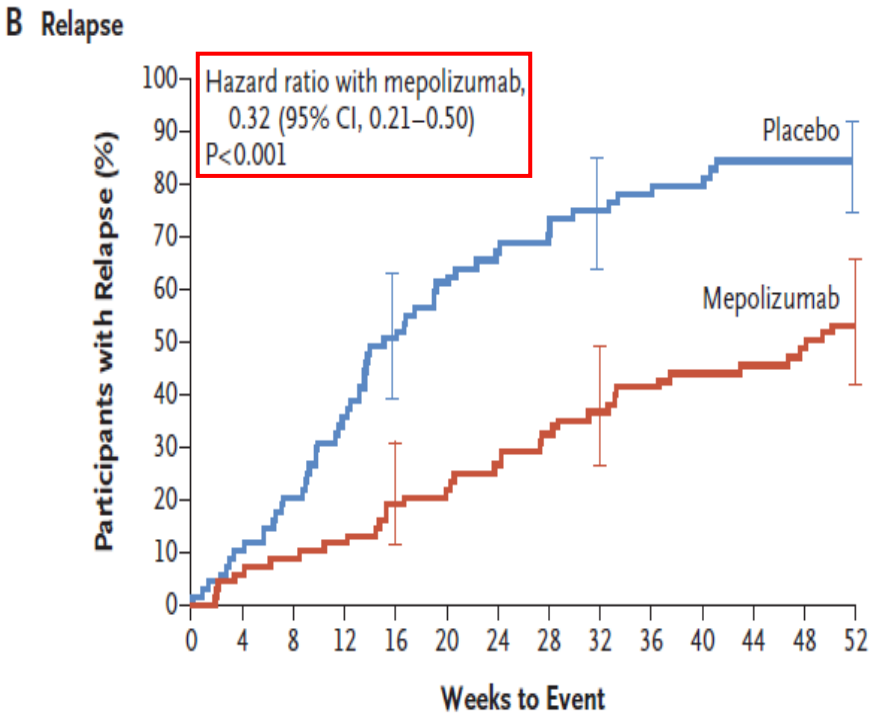
- Randomized, placebo-controlled, double-blind, phase 3 trial
  - at 31 centers across nine countries
- Mepolizumab group (n=68) 300mg SC every 4 weeks + steroid Tx.
- Placebo group (n=68) placebo + steroid Tx.
- Primary end points
  - total accrued weeks of remission
  - the proportion of remission at week 36 and 48



Wechsler et al. N Engl J Med 2017;376:1921-32.

Phase 3 trial of mepolizumab in EGPA





- **44%** of the participants in the **mepolizumab group**, as compared with **7%** of the **placebo group**, had an average daily dose of **prednisolone of 4.0 mg or less** per day during weeks 48 through 52

Wechsler et al. N Engl J Med 2017;376:1921-32.

The effect of reslizumab in EGPA

- Open-label pilot study
- EGPA (10 patients)

- Reslizumab 3mg/kg IV every 4 weeks for 24 weeks

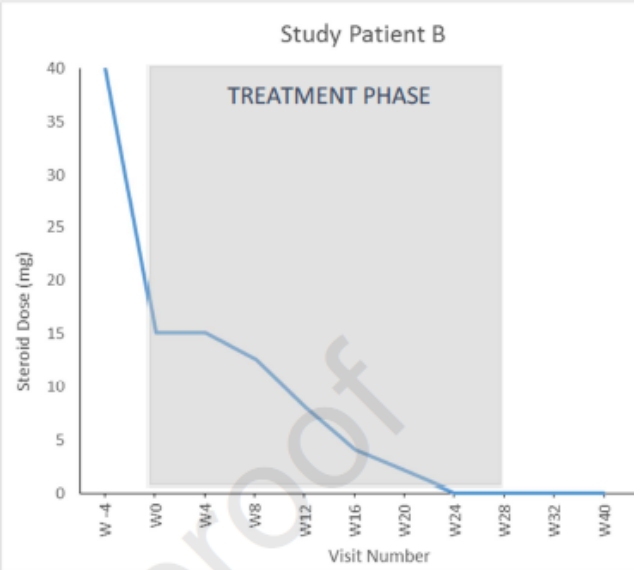
- Primary end points
  - Efficacy (steroid dose reduction, EGPA exacerbation, biomarker…)
  - Safety

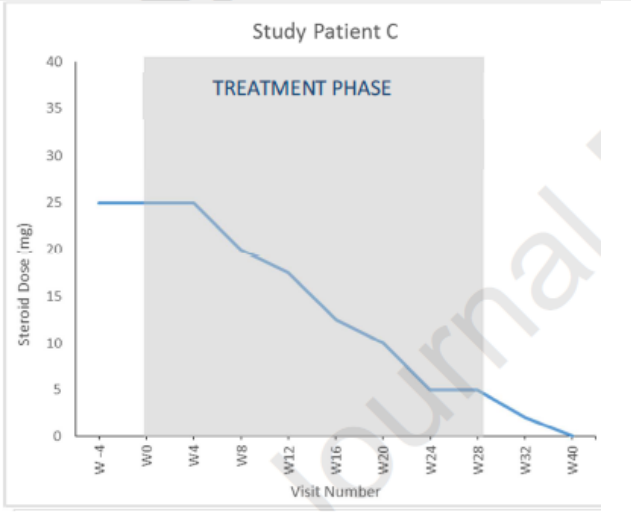
Manka et al. Ann Allergy Asthma Immunol. 2021

The effect of reslizumab in EGPA

Table 4. Steroid Use Outcomes During Trial

	Start of Trial (V1)	End of Trial
Average prednisone use (mg)	17.5	2.5
Lowest prednisone (mg)	10	0
Highest prednisone (mg)	30	10
Number reaching ≤5mg	N/A	6
Number reaching 0mg	N/A	3
>50% reduction in steroids	N/A	7
No exacerbation on therapy	N/A	5





Manka et al. Ann Allergy Asthma Immunol. 2021

The effect of benralizumab in EGPA

- 40 weeks open-label pilot study
- EGPA (10 patients)

- Benralizumab 30mg SC at 4, 8 (monthly) and 16, 24 week (bimonthly)

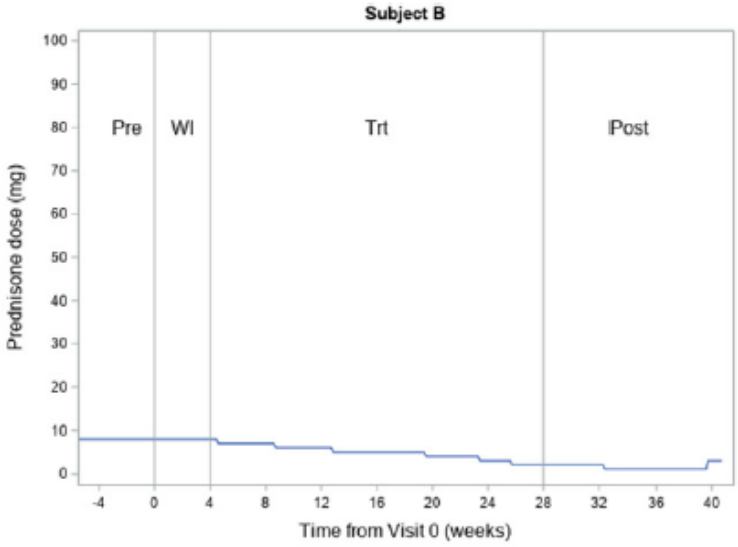
- Primary end points
  - Efficacy (steroid dose reduction, EGPA exacerbation, biomarker…)
  - Safety

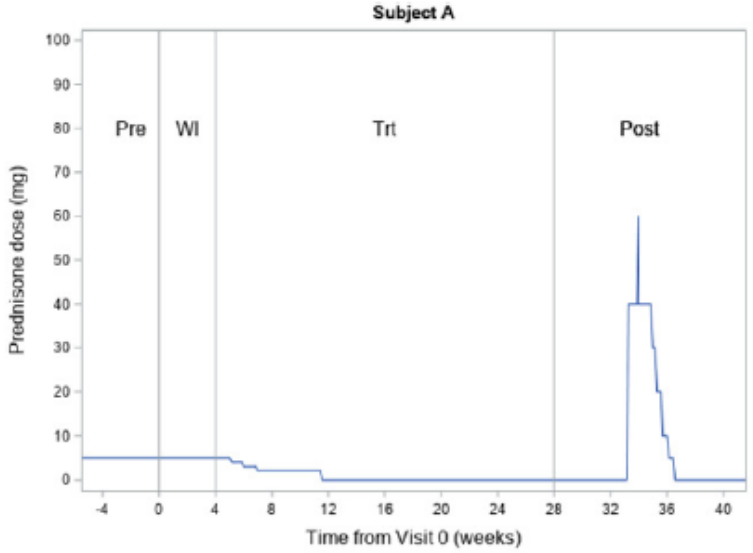
Guntur et al. J Allergy Clin Immunol Pract. 2020

The effect of reslizumab in EGPA

TABLE III. Summary table of outcome variables in all 10 subjects (1 subject removed after week 16 visit, ie, visit 3)

Phase	Prednisone dose (mg)*	Absolute eosinophils*	FEV_1 (% predicted)	FeNO (ppb)*	AQLQ score
Pre	11.6 (6.4, 20.5)	265 (81, 863)	74.5 (61.6, 87.4)	51.9 (33.8, 79.8)	4.9 (3.8, 5.9)
Wash-in	13.4 (3.9, 40.8)	0.04 (−0.8, 4.8)	72.8 (56.8, 88.7)	57.8 (31.6, 105.6)	5.1 (4.0, 6.3)
Treatment	6.3 (3.6, 10.6)	1.1 (−0.2, 4.7)	75.5 (62.9, 88.1)	47.3 (31.8, 70.4)	5.1 (4.1, 6.2)
Post	5.3 (2.6, 9.85)	7.0 (1.5, 24.2)	70.9 (57.9, 83.9)	35.5 (23.1, 54.4)	5.0 (3.9, 6.1)





Manka et al. Ann Allergy Asthma Immunol. 2021;3:1081-206

Conclusions

1. HES and EGPA is a rare but serious systemic disease with eosinophilia.

2. The definition and classification of these diseases are still controversial and evolving in line with the new discovery of pathogenesis.

3. There is not a definite a disease monitoring marker in both HES and EGPA. Eosinophil granule protein and other pathognomonic molecule can be a potential candidate to these diseases.

4. Anti IL-5 therapy such as mepolizumab, reslizumab or benralizumab should be considered in new treatment option.