Syndromes Hyperéosinophiles

Florence ROUFOSSE
Hôpital Erasme, Bruxelles, Belgique

28 et **29** SEPTEMBRE 2021

UIC-P - Espaces Congrès - 16, rue Jean Rey - 75015 Paris

Sous l'égide de :

Plan de l'Atelier

(Définition d'une hyperéosinophilie et causes classiques)

Définition et Classification des Syndromes Hyperéosinophiles

Variantes d'intérêt : selon la physiopathologie sous-jacente / tableau clinique

Comment je diagnostique :

- variantes, outils diagnostiques
- recherche de complications

Comment je traite :

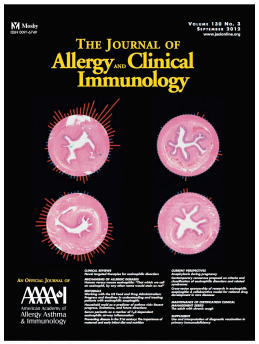
- stratégie thérapeutique selon la variante
- agents thérapeutiques classiques et nouveaux

Définition d'une hyperéosinophilie

Current perspectives

Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

Peter Valent, MD,[a] Amy D. Klion, MD,[b] Hans-Peter Horny, MD,[c] Florence Roufosse, MD, PhD,[d] Jason Gotlib, MD,[e] Peter F. Weller, MD,[f] Andrzej Hellmann, MD,[g] Georgia Metzgeroth, MD,[h] Kristin M. Leiferman, MD,[i] Michel Arock,



SEPTEMBER 2012
VOLUME 130, NUMBER 3

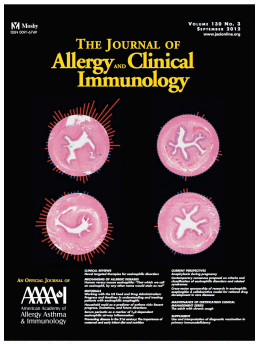
Blood, Counts x 10^9/L Blood[2]	
Hypereosinophilia	>1.5 recorded on ≥2 determinations with a minimum time interval of 4 weeks
Eosinophilia	0.5 - 1.5
Normal	0.05 – 0.5 (1% - 6% WBC)
Tissue	
The percentage of eosinophils >20% of all nucleated bone marrow cells AND/OR	
Pathologist is of the opinion that tissue eosinophil infiltration is excessive compared with the normal physiological range, compared with other inflammatory cells or both AND/OR	
A specific eosinophil granule protein[a] stain demonstrates extensive extracellular deposition indicative of local eosinophil activation and degranulation even in the absence of local eosinophil infiltration	

Définition d'une hyperéosinophilie

Current perspectives

Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

Peter Valent, MD,[a] Amy D. Klion, MD,[b] Hans-Peter Horny, MD,[c] Florence Roufosse, MD, PhD,[d] Jason Gotlib, MD,[e] Peter F. Weller, MD,[f] Andrzej Hellmann, MD,[g] Georgia Metzgeroth, MD,[h] Kristin M. Leiferman, MD,[i] Michel Arock,

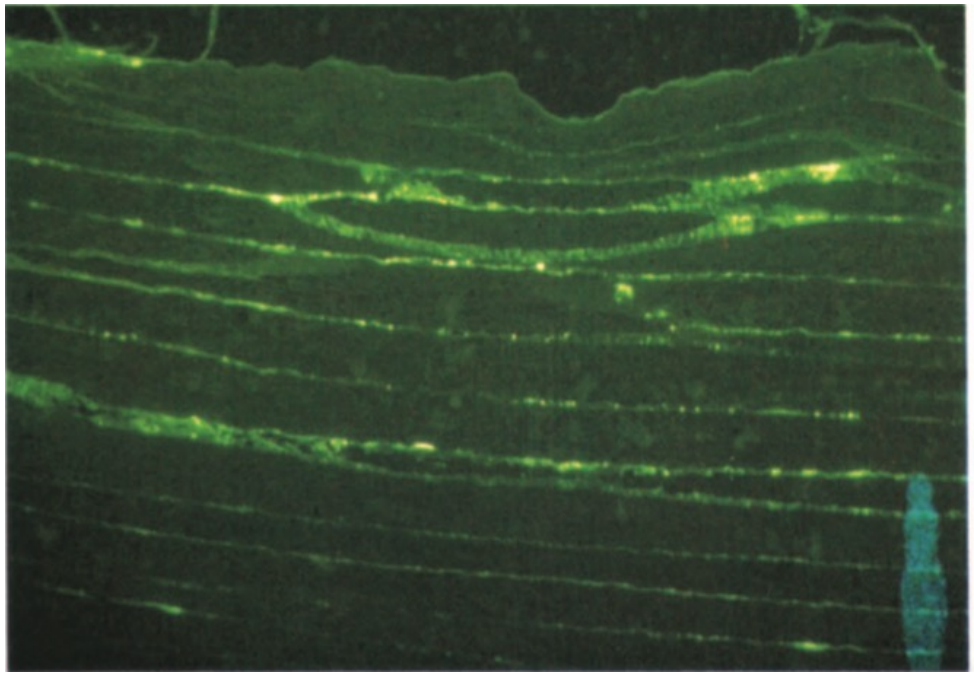


SEPTEMBER 2012
VOLUME 130, NUMBER 3

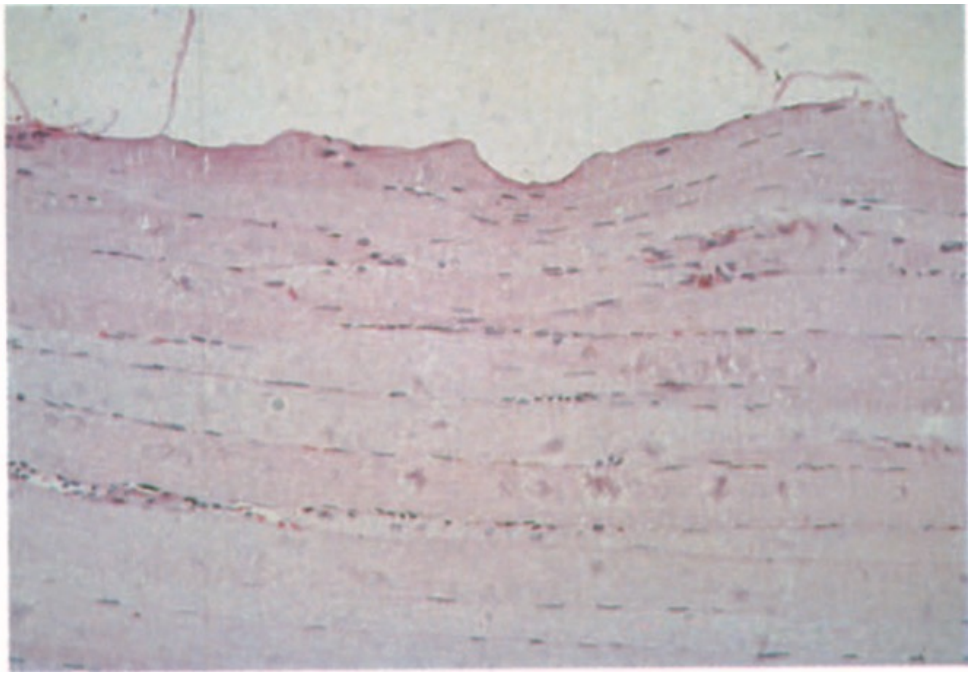
Blood, Counts x 10^9/L Blood[2]	
Hypereosinophilia	>1.5 recorded on ≥2 determinations with a minimum time interval of 4 weeks
Eosinophilia	0.5 - 1.5
Normal	0.05 – 0.5 (1% - 6% WBC)
Tissue	
The percentage of eosinophils >20% of all nucleated bone marrow cells AND/OR	
Pathologist is of the opinion that tissue eosinophil infiltration is excessive compared with the normal physiological range, compared with other inflammatory cells or both AND/OR	
A specific eosinophil granule protein[a] stain demonstrates extensive extracellular deposition indicative of local eosinophil activation and degranulation even in the absence of local eosinophil infiltration	

Dépôt extracellulaire de granules/protéines

Major basic protein



Hematoxyline & Eosine



Causes classiques d'HE

Allergie médicamenteuse

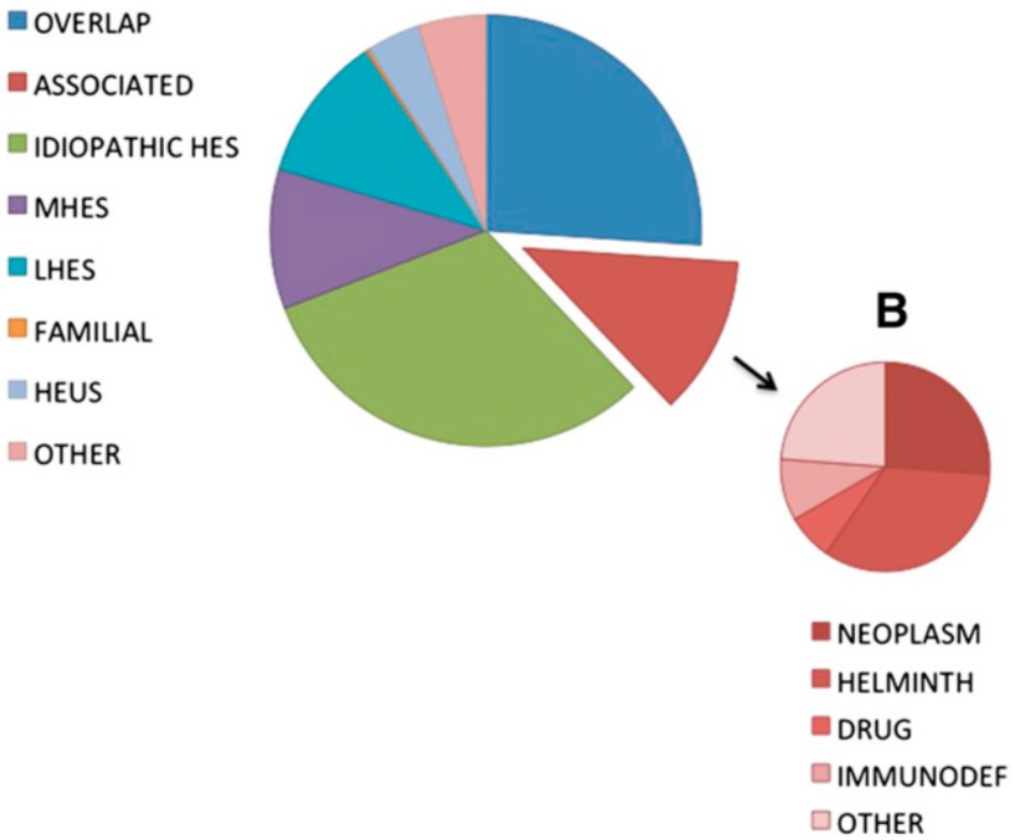
Infection parasitaire : helminthiase, ectoparasites

Affection néoplasique : tumeur solide / hémopathie

Autres …

maladies auto-immunes, immunodéficiences primaires, ... … …

Causes classiques d'HE



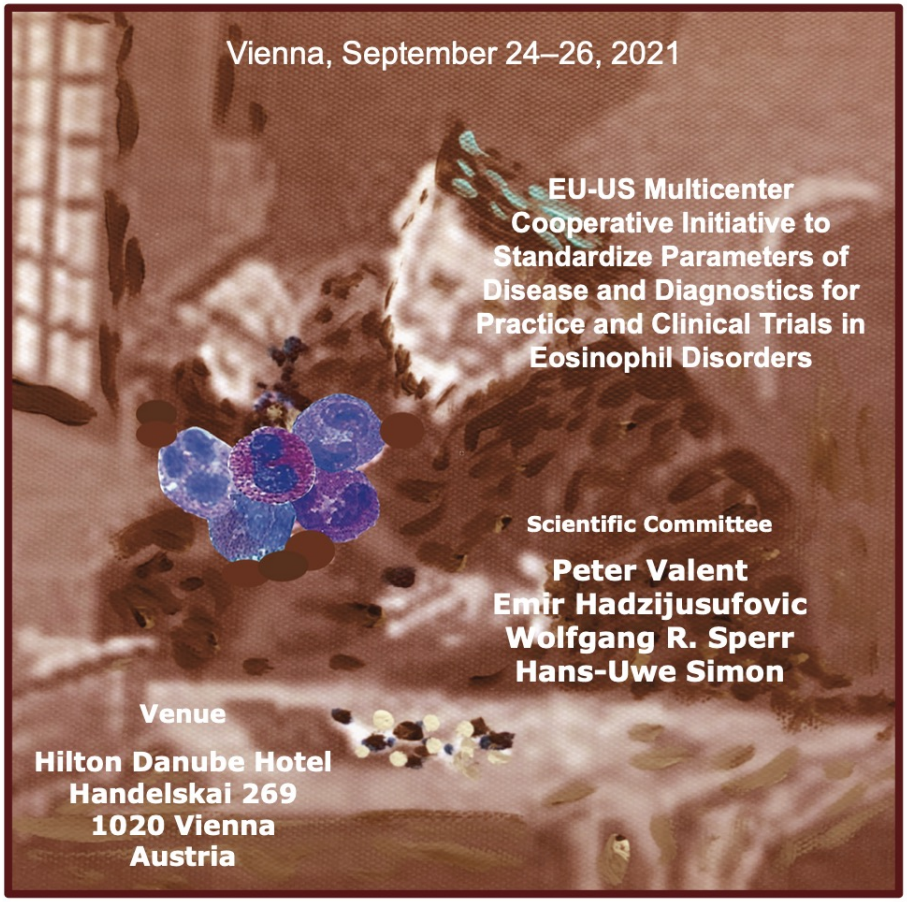
Klion, Blood 2015; 126 (9): 1069

Définition des Syndromes Hyperéosinophiles

Proposed term	Proposed abbreviation	Definition and criteria
Blood eosinophilia	—	>500 Eosinophils × 10^9/L blood
Hypereosinophilia	HE	>1500 Eosinophils × 10^9/L blood on 2 examinations (interval ≥1 month*) and/or tissue HE defined by the following†: 1. Percentage of eosinophils in BM section exceeds 20% of all nucleated cells and/or 2. Pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or 3. Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils).
Hypereosinophilic syndrome	HES	1. Criteria for peripheral blood HE fulfilled* and 2. Organ damage and/or dysfunction attributable to tissue HE‡ and 3. Exclusion of other disorders or conditions as major reason for organ damage.
Eosinophil-associated single-organ diseases		1. Criteria of HE fulfilled and 2. Single-organ disease (see Table III and Tables E4 and E5 for specific entities)

Définition des Syr

Year 2021 Working Conference on Eosinophil Disorders and Related Syndromes



Proposed term	Proposed abbreviation
Blood eosinophilia	—
Hypereosinophilia	HE
Hypereosinophilic syndrome	HES
Eosinophil-associated single-organ diseases	

ıonth*) and/or tissue HE defined by

ıucleated cells and/or
hils is extensive and/or
the absence or presence of major tissue

nd
organ damage.

specific entities)

Complications d'une HE persistante

General
fatigue, myalgia, weight loss, fever

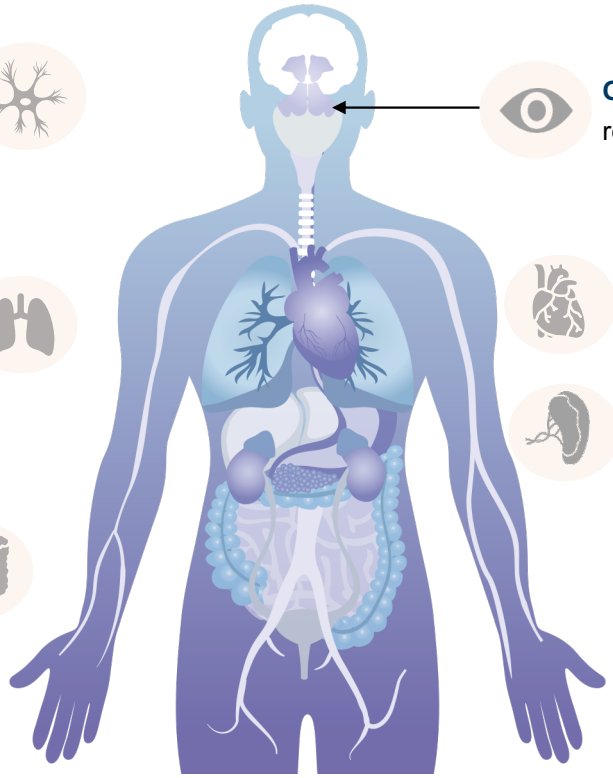
Neurological
embolic stroke, encephalitis, peripheral neuropathy

Pulmonary
asthma, eos. lung infiltrates, fibrosis

Hepatic
hepatitis, cholangitis

Gastrointestinal
(gastro-)enteritis, colitis

Vascular
art./ven. thrombosis, microvascular damage, vasculitis



Ocular
retinal micro-emboli, choroidal inflammation

Sino-nasal cavities
chronic rhino-sinusitis, polyposis

Cardiac
myocarditis, intracavitary thrombus, subendocardial fibrosis, valve entrapment, pericarditis

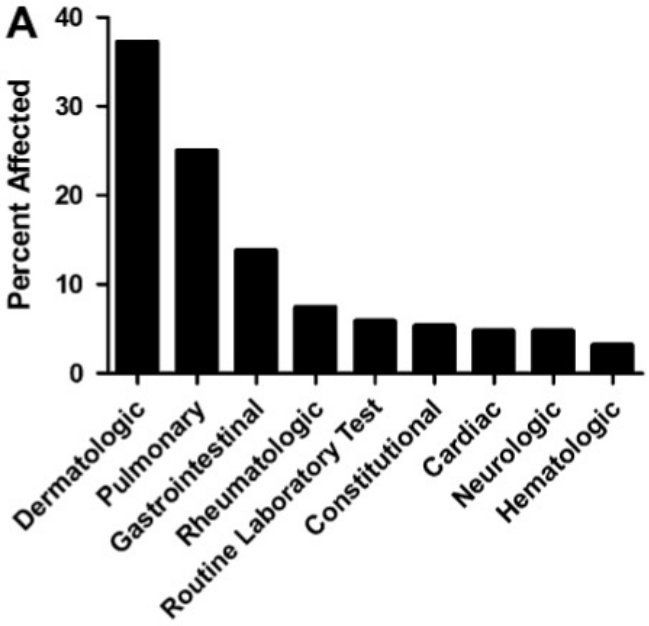
Splenic
splenomegaly

Dermatologic
pruritis, eczema, dermatitis, urticaria, erythroderma

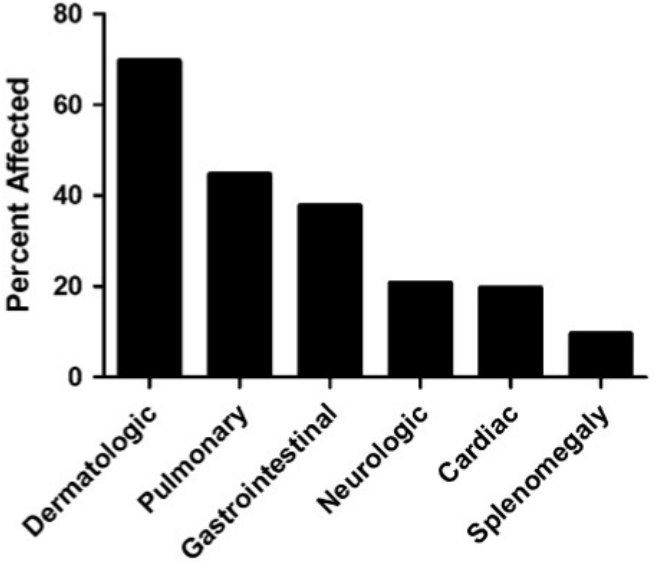
Soft tissue / Rheumatological
angioedema, fasciitis, myositis, synovitis, arthritis

Complications d'une HE persistante

Présentation initiale



Au cours du temps



Ogbogu et al, JACI 2009; 124(6): 1319

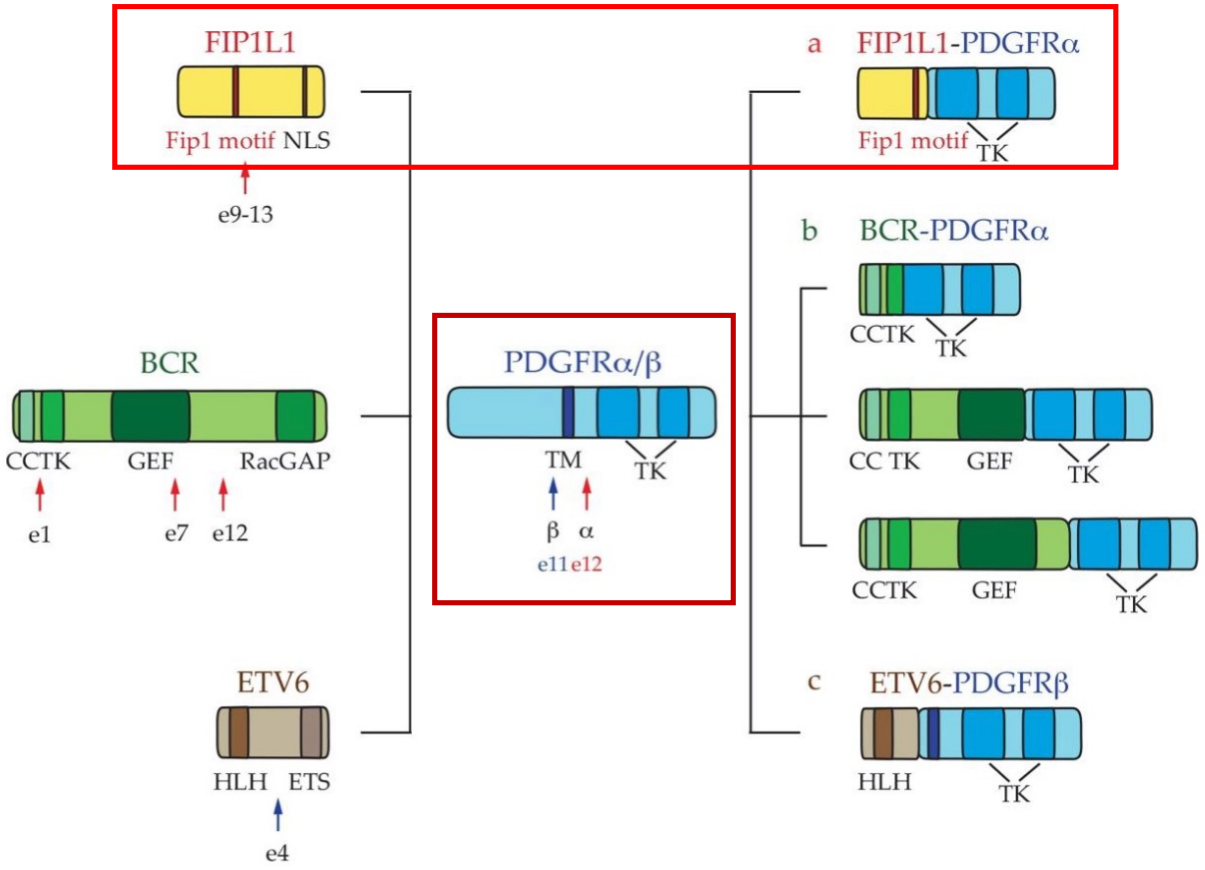
Hyperéosinophilie de signification indéterminée

Proposed terminology	Proposed abbreviation
Hereditary (familial) HE	HE_{FA}
HE of undetermined significance	HE_{US}
Primary (clonal/neoplastic) HE†	HE_{N}
Secondary (reactive) HE†	HE_{R}

Classification des Syndromes Hyperéosinophiles

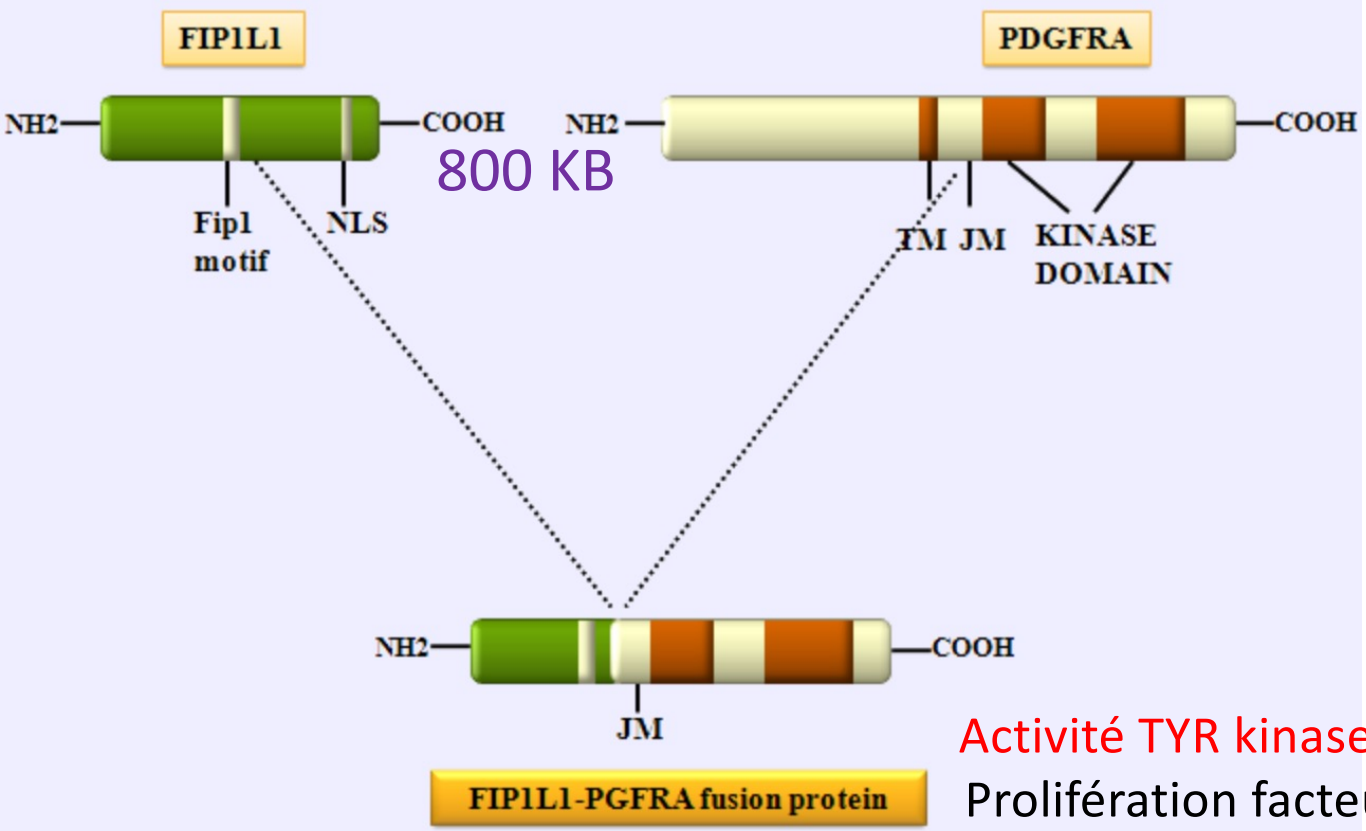
Primaire	Secondaire	Idiopathique
Eosinophilie clonale, néoplasique (HES_N)	Eosinophilie réactionnelle (HES_R)	Mécanisme sous-jacent inconnu (HES_{Id})

HES primaire – néoplasique (HES_N)



Fusion FIP1L1-PDGFRA

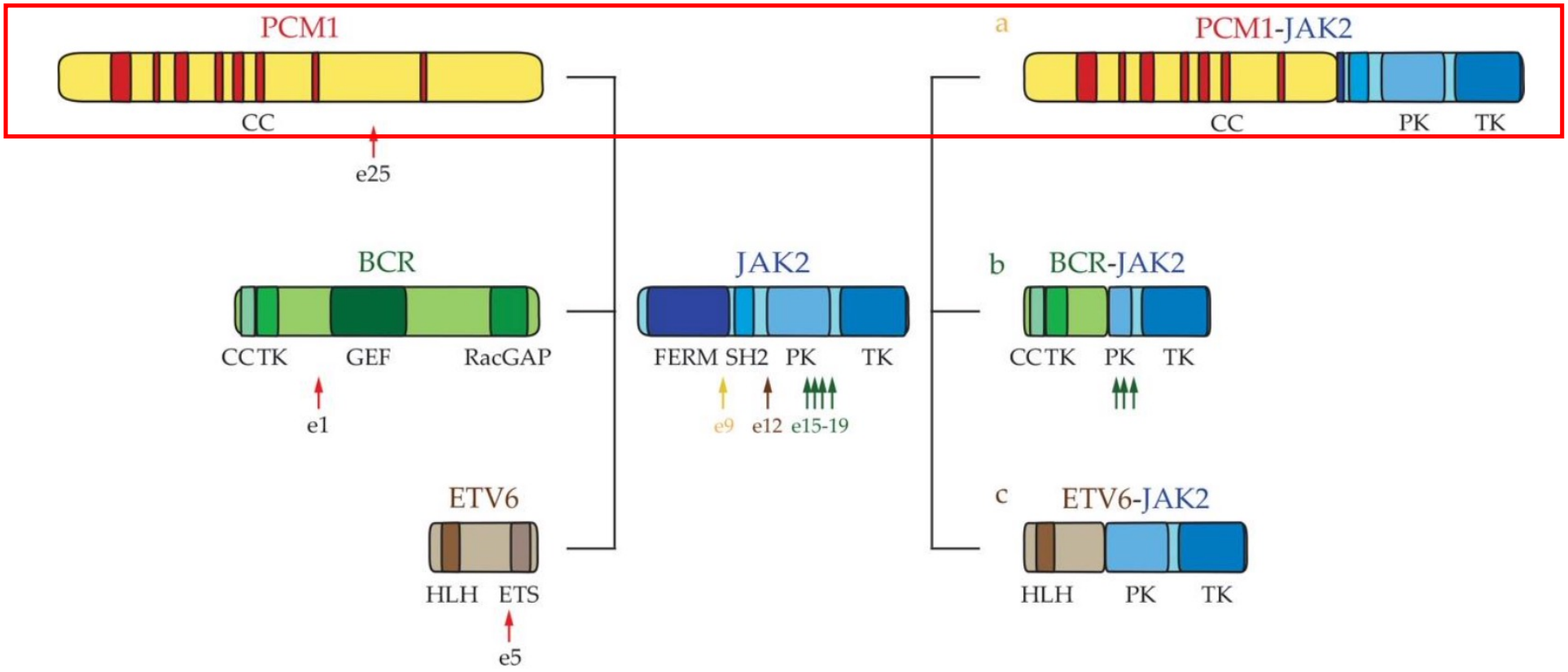
CHROMOSOME 4 - BRAS LONG



Activité TYR kinase autonome

Prolifération facteur-indépendante

Fusions impliquant JAK2



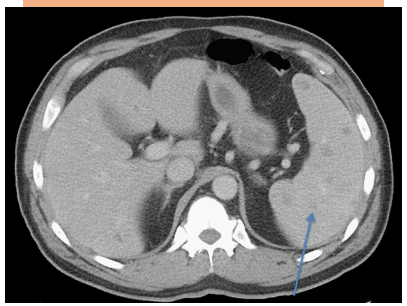
HES_N - quand y penser?

Sexe masculin (PDGFR)

Vitamine B12 et/ou tryptase sérique élevée(s)

HE résistante aux corticostéroïdes

Splénomégalie



Perturbations autres lignées, formes jeunes circulantes

Anémie
Thrombocytopénie

Mastocytose et hyperéosinophilie

- Diagnostic différentiel en cas de tryptase élevée
- L'hyperéosinophilie peut être clonale ou réactionnelle
- La détection d'une mutation D816V dans le sang peut s'expliquer par l'éosinophilie clonale

HES secondaire – réactionnel (HES_R)

Mécanisme sous-jacente bien identifiable
Traitement/prise en charge spécifique

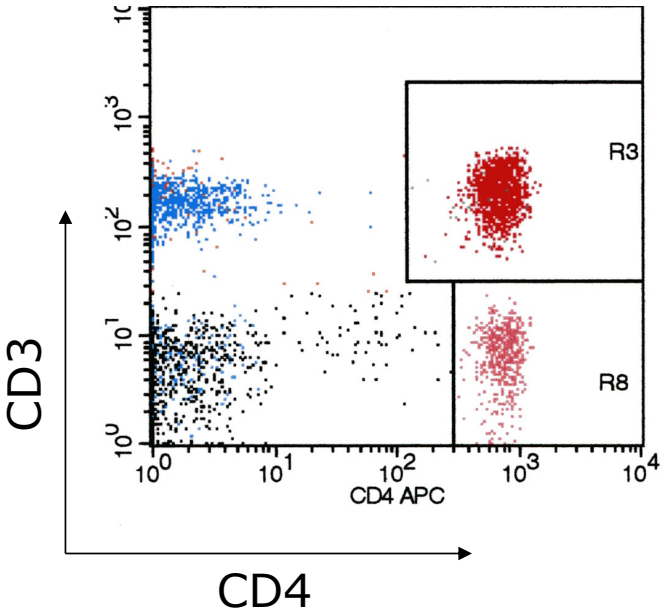
Helminthiase
DRESS (allergie médic)
Cancer solide (poumon, cervix …)
Lymphome T (Hodgkin, λB)
Pemphigoïde bulleuse
… … … …

Mécanisme sous-jacent implique surproduction de facteurs éosinophilopoïétiques mais peu/pas caractérisé
Traitement visant à réduire l'inflammation

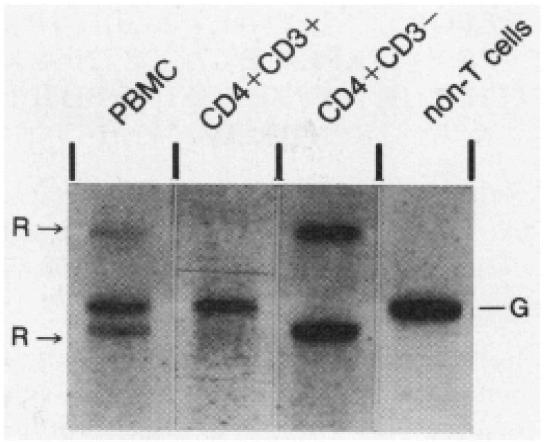
Variant lymphoïde du HES
… … … …

Variant lymphoïde du HES

Immunophénotypage lymphocytaire



Réarrangement TCR



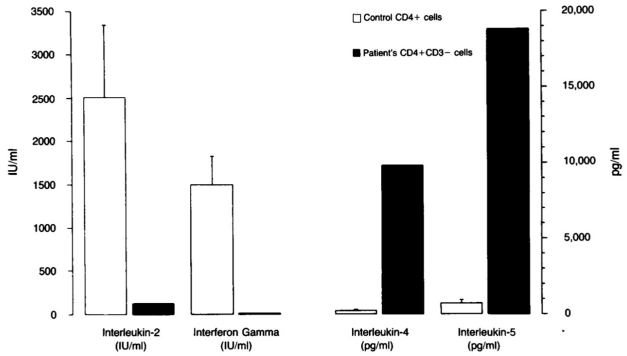
. Southern Blot Analysis of Gene Coding for the β Chain of the T-Cell Receptor.

Profil cytokinique in vitro

Spontané

Cells	Interleukin-2	Interferon Gamma	Interleukin-4	Interleukin-5
	IU/ml		*pg/ml*	
Patient				
Total CD4+	<0.1	<0.2	47	266
CD4+CD3−	<0.1	<0.2	71	430
Controls				
Total CD4+	<0.1	<0.2	<4	<10

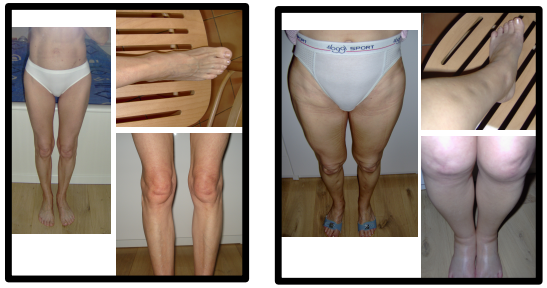
Après stimulatation



Cogan et al, N Engl J Med 1994; 330(8): 535

HES_R - quand y penser?

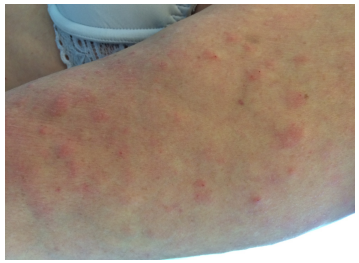
Angioedème



HE prolongée asymptomatique (HE_{US})

Ténosynovite
Fasciite

Lésions cutanées prurigineuses

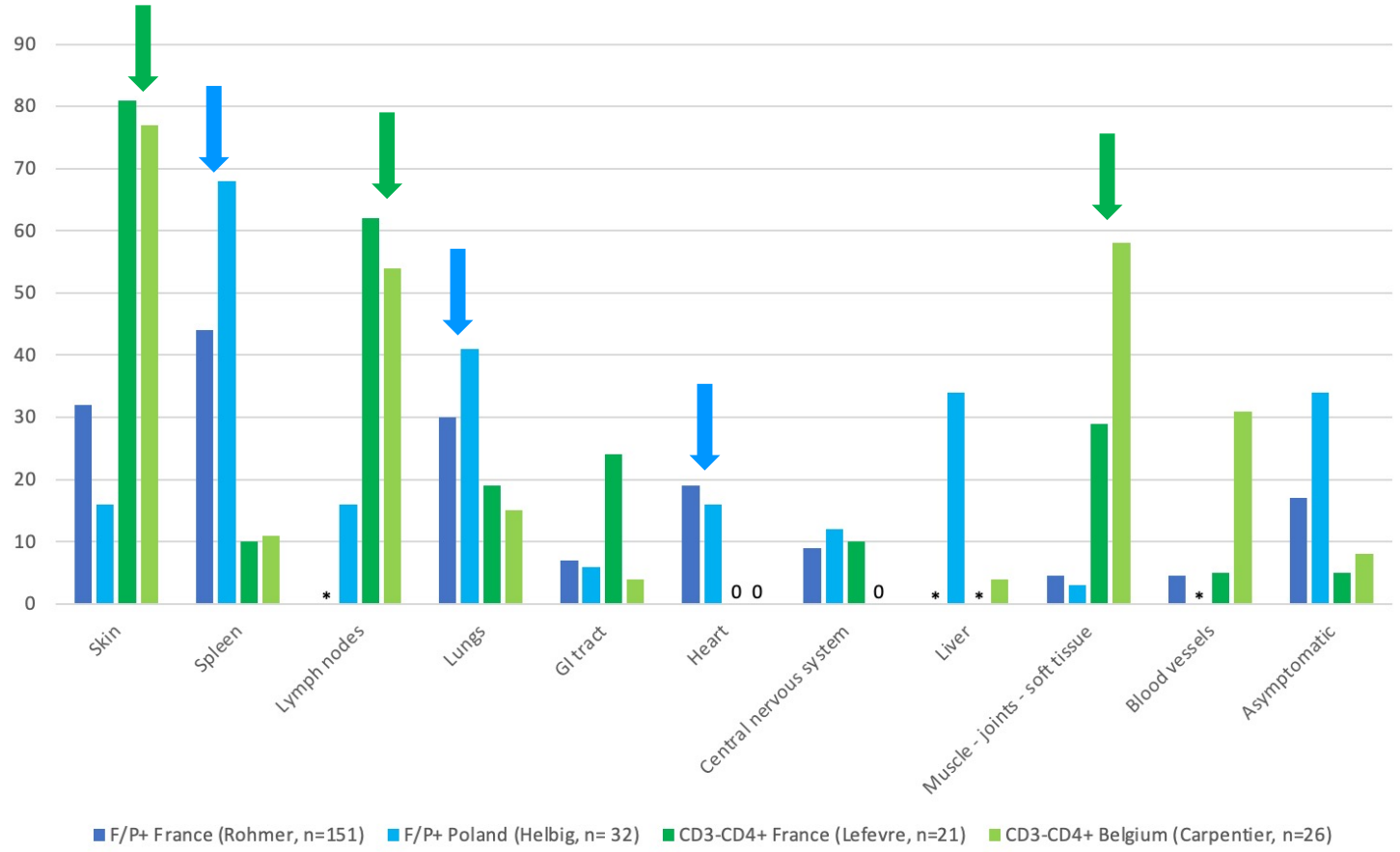


Petites adénopathies disséminées, à activité métabolique légère à modérée

HyperIgM

HyperIgE marquée

Définition


90
80
70
60
50
40
30
20
10
0
Skin
Spleen
Lymph nodes
Lungs
GI tract
Heart
Central nervous system
Liver
Muscle - joints - soft tissue
Blood vessels
Asymptomatic
F/P+ France (Rohmer, n=151)
F/P+ Poland (Helbig, n= 32)
CD3-CD4+ France (Lefevre, n=21)
CD3-CD4+ Belgium (Carpentier, n=26)

HES idiopathique

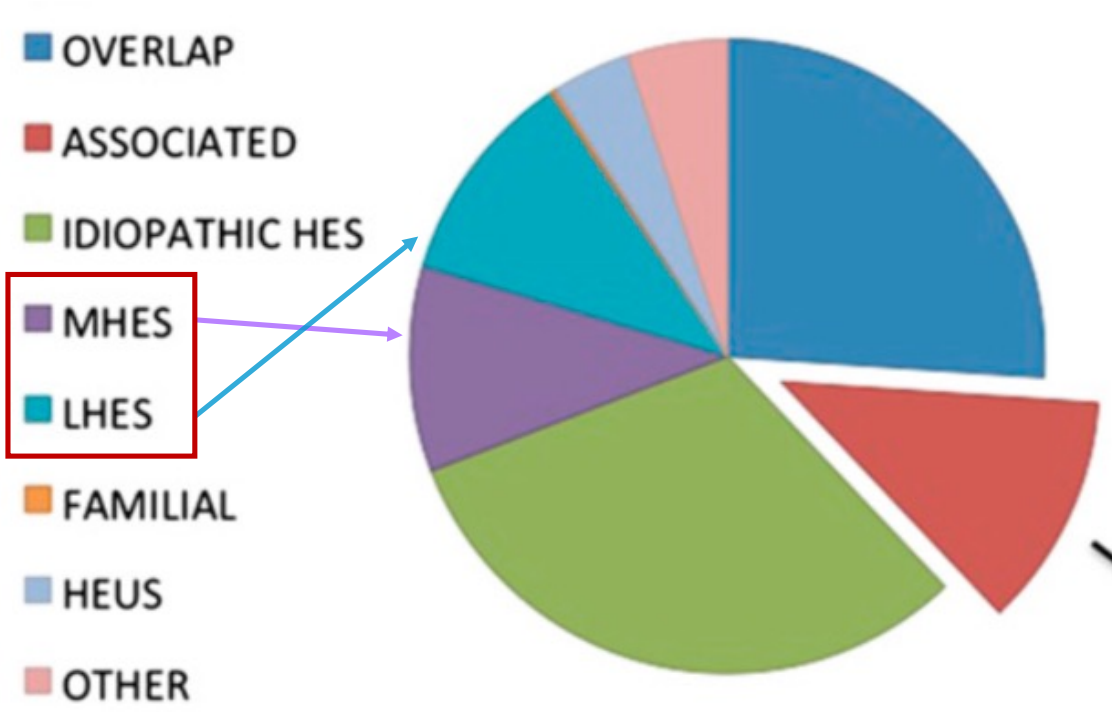
- Ceux qui restent ….
- Hétérogénéité +++
  - Mécanismes pathogènes (inconnus)
  - Présentation clinique (systémique, spécifique d'organe)

Klion. Annual Rev Med 2009; 60: 293

Table 2 Diagnosis of selected HES variants[a]

Myeloproliferative variant
Definitive
F/P or another PDGFRA fusion by RT-PCR, FISH, or other methods
eosinophil clonality by HUMARA analysis, karyotype, or other modality
Presumptive
≥4 of the following:
increased serum tryptase level
increased serum B12 level
splenomegaly
anemia, thrombocytopenia
increased circulating myeloid precursors
dysplastic eosinophils
myelofibrosis
increased spindle-shaped mast cells in the bone marrow
clinical and hematologic response to imatinib or other tyrosine kinase inhibitors
Lymphoproliferative variant
Definitive
phenotypically aberrant T cell population[b]
clonal T cell rearrangement pattern by PCR
increased T cell production of eosinophilopoietic cytokines
Supportive
increased serum TARC
increased serum IgE
predominantly cutaneous manifestations
history of atopy
steroid-responsive

Fréquence relative des variantes du HES



Investigation d'une HE inexpliquée: les complications

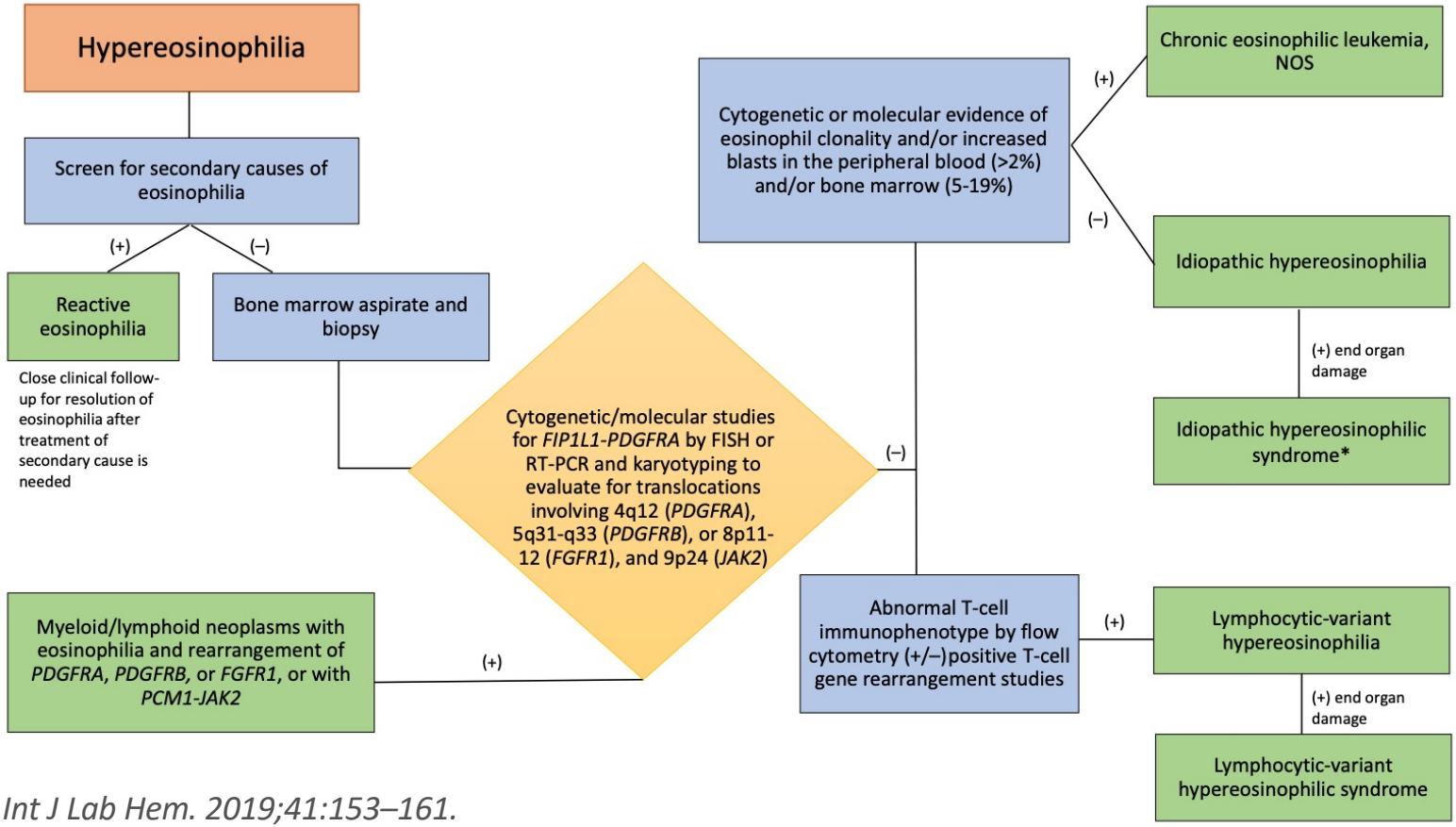
Cardiaques: troponine sérique, ECG, échographie cardiaque, IRM ++
d'office !! (biopsie rarement indiquée)

Pulmonaires: EFR, CT thorax, endoscopie (LBA, BTB)
Digestives: endoscopies avec biopsies, CT abdomen (+C), biopsie hépatique
Cutanées: biopsie ++
Neurologiques: IRM cérébrale, VCN
Hématologiques: CT abdomen (organomégalie)
Rhumatologiques / Tissus mous: échographie, ponction articulaire, IRM membres
Vasculaires: échographie (thromboses veineuses), angiographie

… … …

L'examen clinique attentif est primordial et guidera les investigations

Investigation d'une HE inexpliquée: les variantes

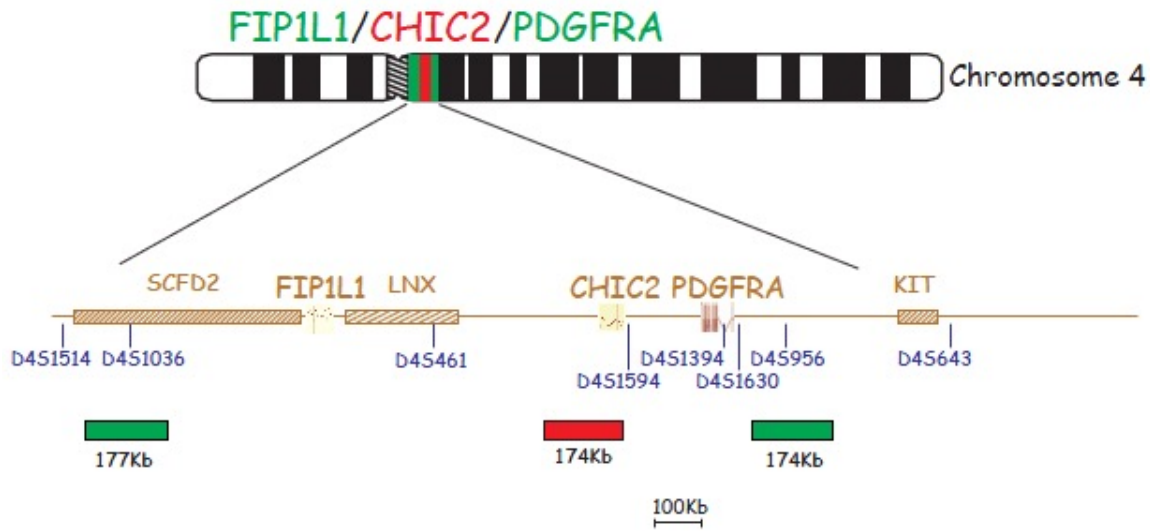


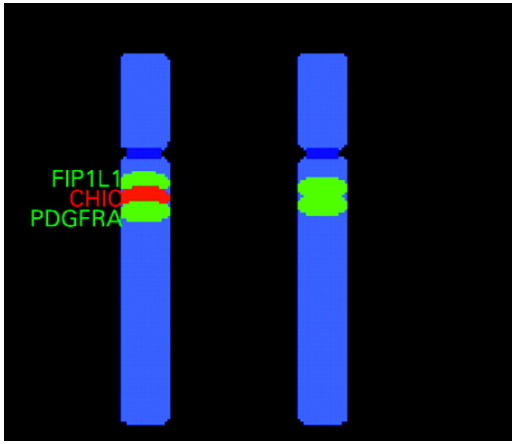
Larsen and Savage. Int J Lab Hem. 2019;41:153–161.

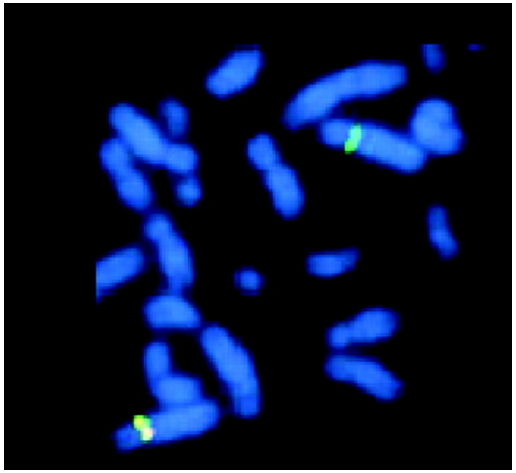
Investigation d'un variant myéloïde

Gène de fusion FIP1L1-PDGFRA
- PCR (problème de breakpoints)
- FISH CHIC2

(sang et/ou moëlle)







Investigation d'un variant myéloïde, suite

Cytologie sur sang périphérique et sur moëlle: dysplasie

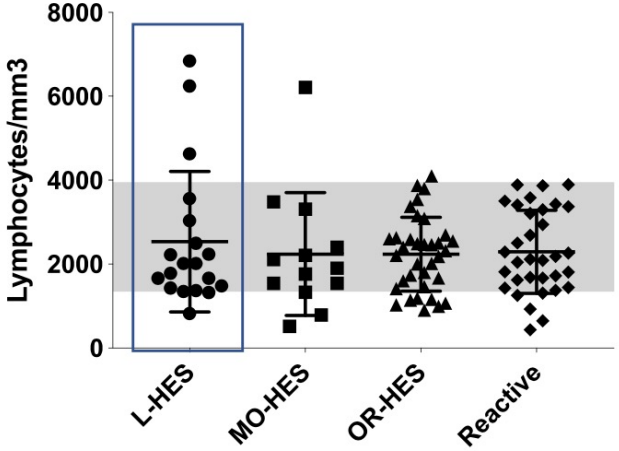
Karyotype

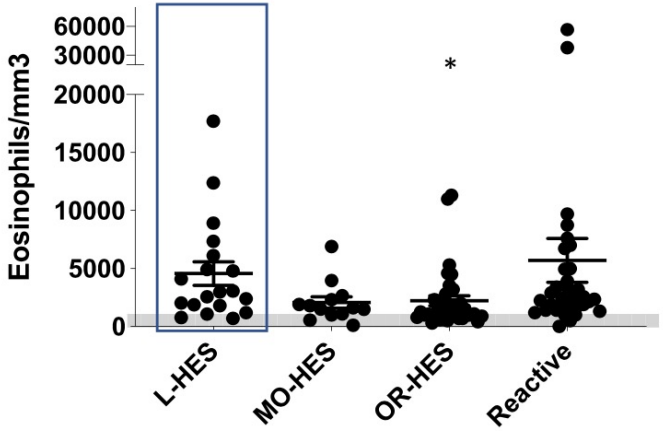
PCR orientées (PDGFRB, FGFR1, JAK2)

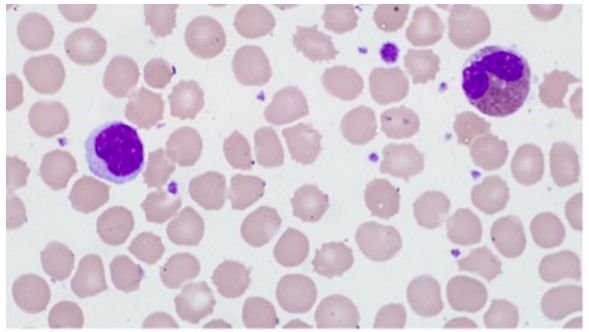
En présence d'éléments cliniques suggestifs d'un néoplasme myéloïde:

NGS panel myéloïde > détection de polymorphismes sur gènes d'intérêt

Investigation d'un variant lymphoïde





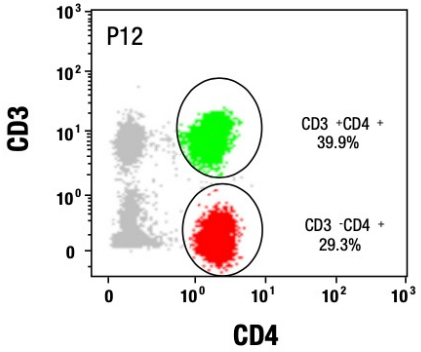


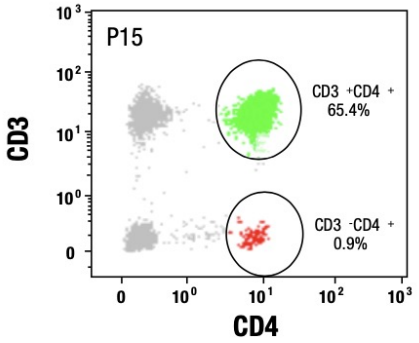
Carpentier et al, J Allergy Clin Immunol Pract 2021; 9:2426.

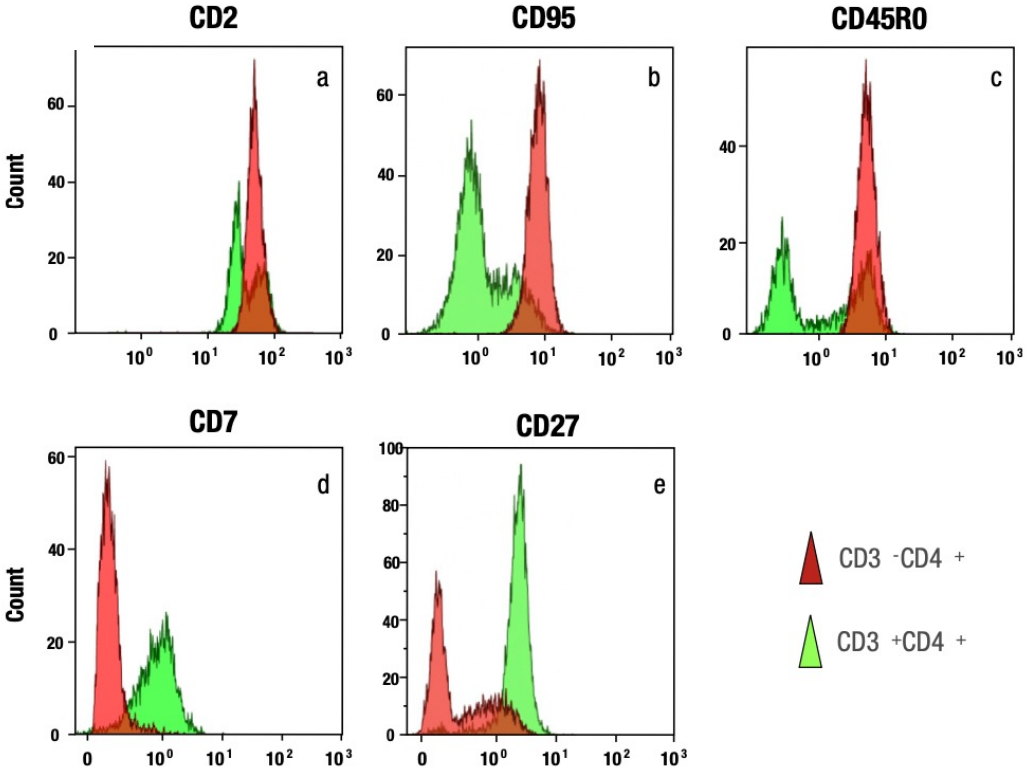
Investigation d'un variant lymphoïde: CD3^{-}CD4^{+}

Détection des LT CD3^{-}CD4^{+}

- Phénotypage lymphocytaire (sang et/ou moëlle)







Carpentier et al, J Allergy Clin Immunol Pract 2021; 9:2426.

Investigation d'un variant lymphoïde: $CD3^{-}CD4^{+}$

Attention au diagnostic différentiel avec un lymphome T

Sezary – Mycosis fungoïdes

Lymphome T angioimmunoblastique ++

ATLL (HTLV)

PTCL-NOS

Les LT CD3-CD4+ du L-HES n'expriment pas les marqueurs CD10, PD-1, ICOS, CXCL13

Et les autres populations lymphocytaires aberrantes?

CD3+CD4-CD8-

CD3+CD4+CD7-

Autres ?

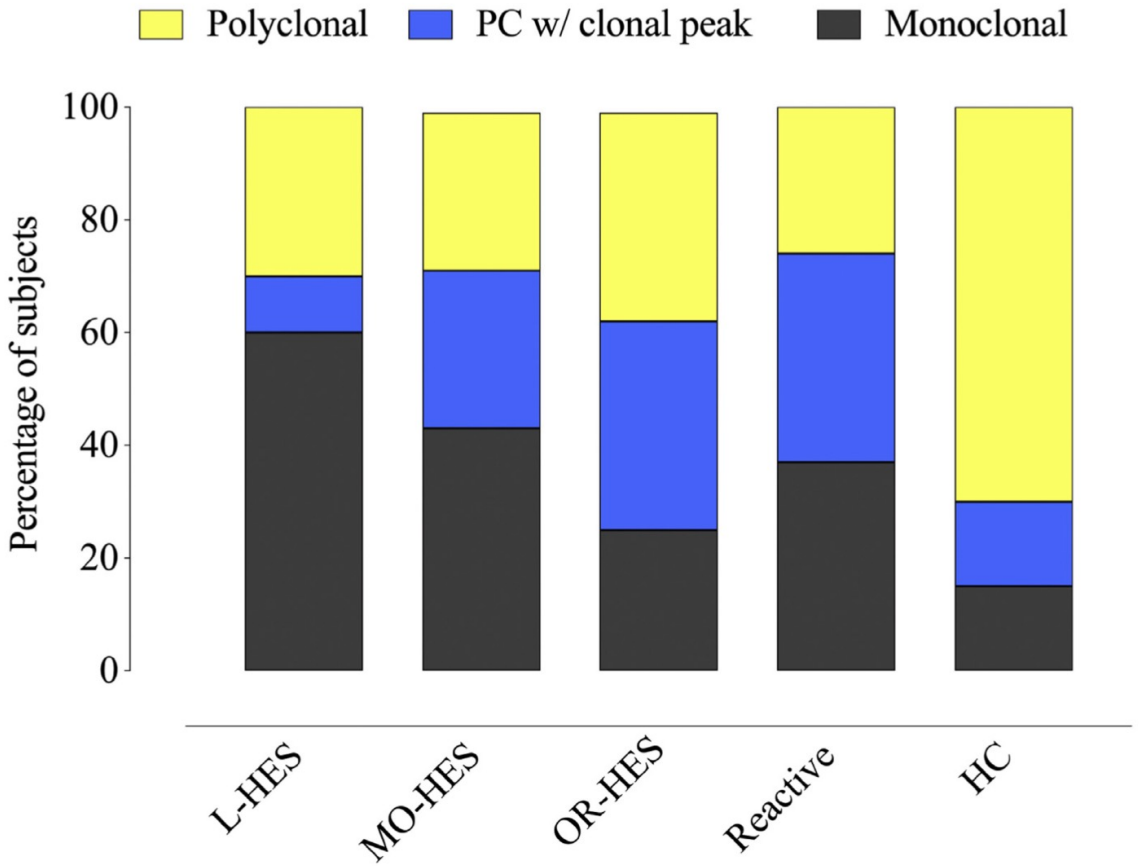
Panel TCR Vbeta, sur-/sous-expression de marqueurs T (CD2,CD5, CD6, CD7 …)

?? Signification clinique

Idéalement démontrer la causalité en investiguant le profil cytokinique

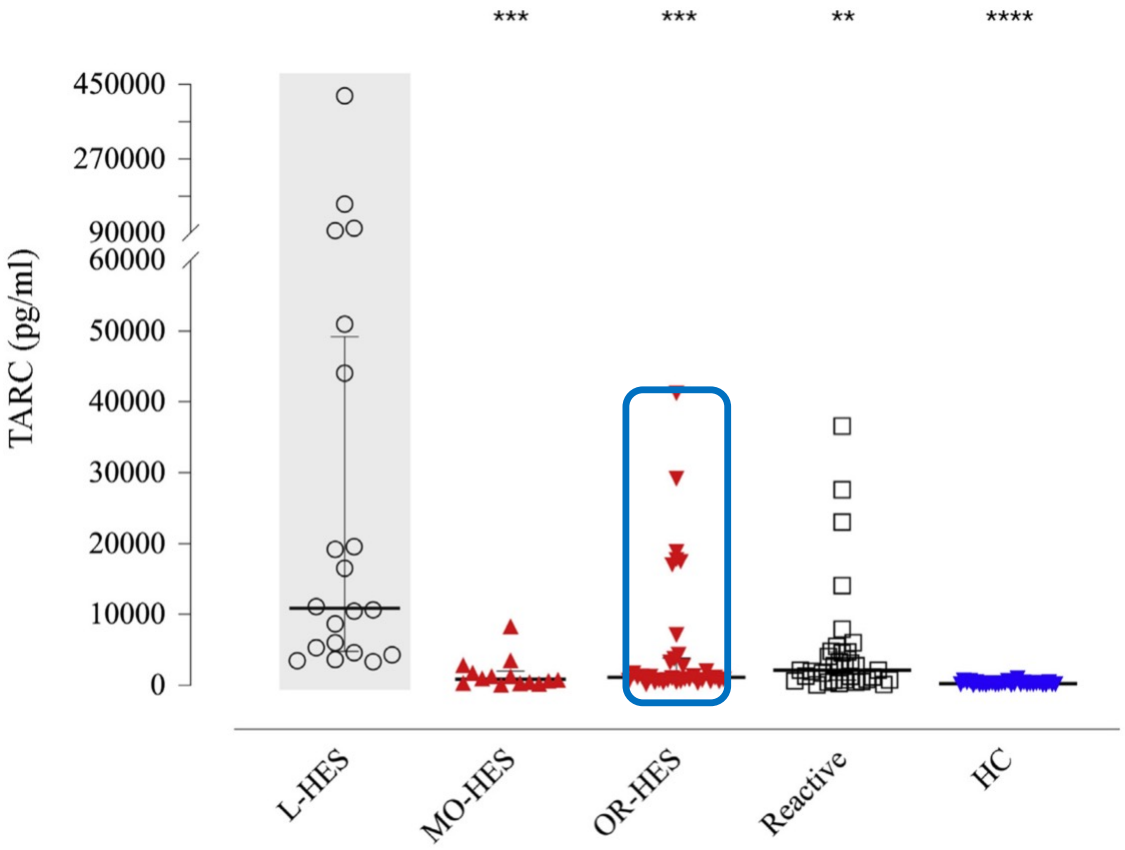
À défaut, « accumuler l'évidence » … recherche de clonalité, dosage CCL17/TARC sérique

Manque de spécificité de l'étude de clonalité (pattern TCR)

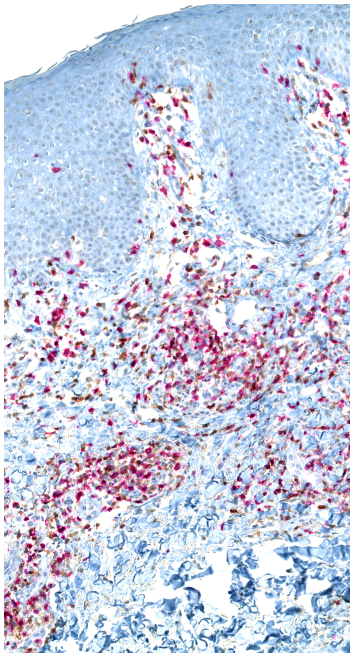


Carpentier et al, J Allergy Clin Immunol Pract 2021; 9:2426.

Quantification du CCL17/TARC sérique



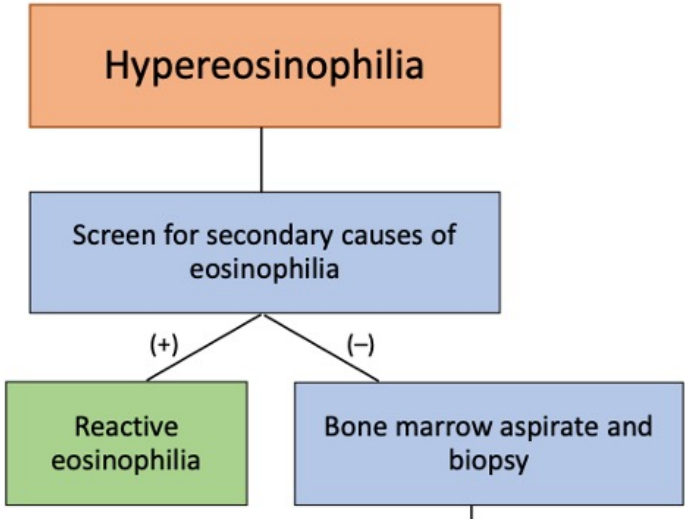
CD4 CD8



Carpentier et al, J Allergy Clin Immunol Pract 2021; 9:2426.

Quand faire une ponction sternale / biopsie ostéo-médullaire?

Hématologues



Immunologistes

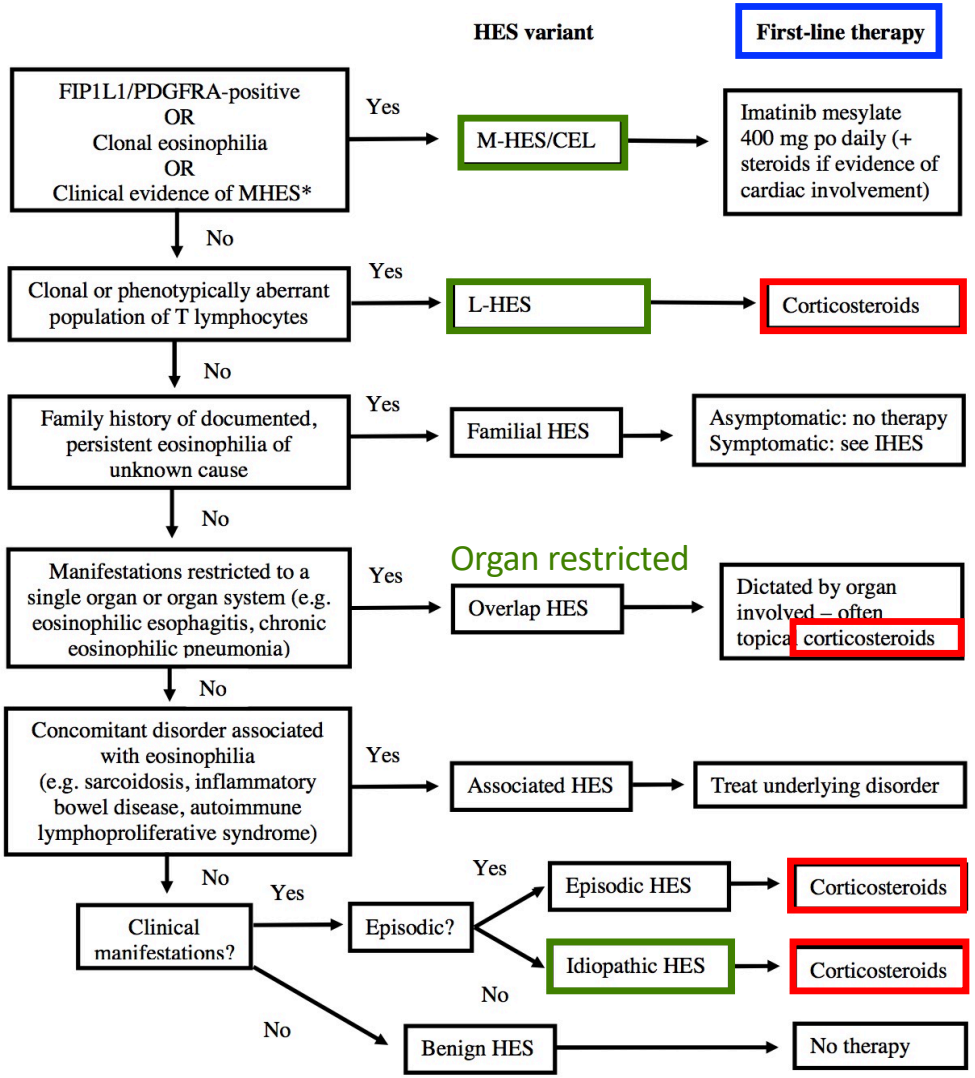
Table 2. Diagnostic studies

Test	Comment
Bone marrow biopsy, including cytogenetics*	Recommended in all patients with AEC $> 5.0 \times 10^9$/L and features of M-HES or L-HES. Should be considered in other patients

Tryptase élevée

Prise en charge thérapeutique

Première ligne



Adapted from Klion Blood 2009; 114: 3736

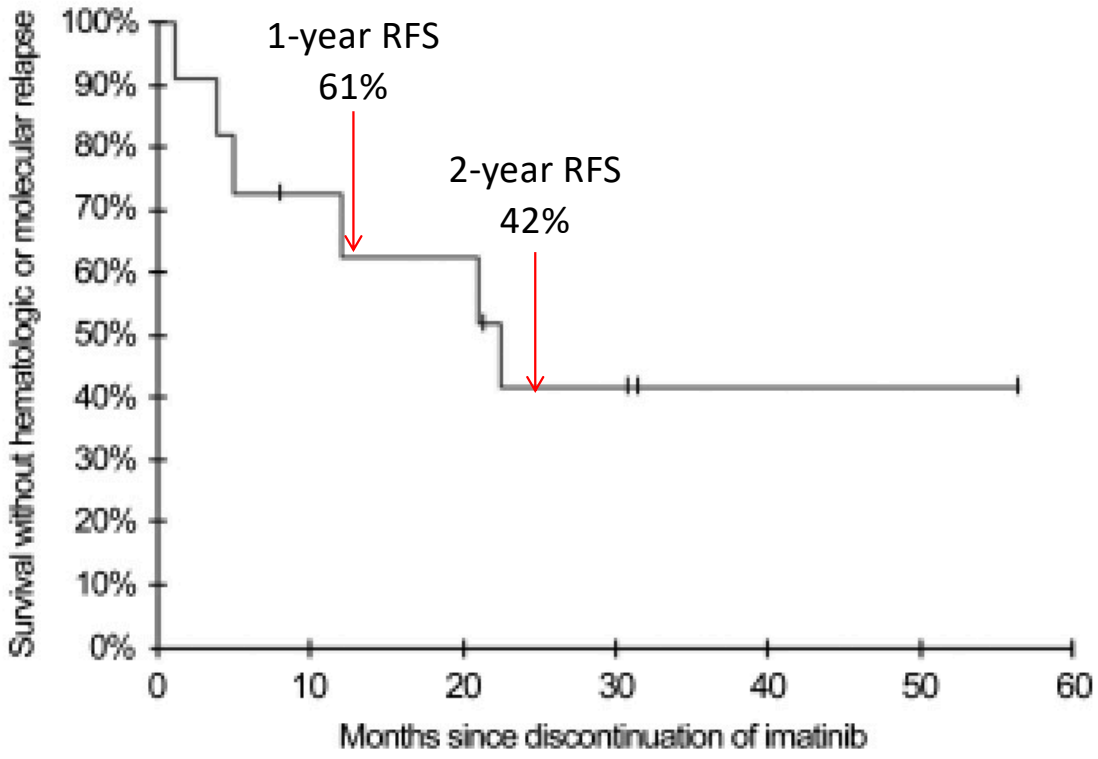
FIP1L1-PDGFRA : Imatinib mesylate

TABLE 3. Dose and Response to Imatinib Treatment

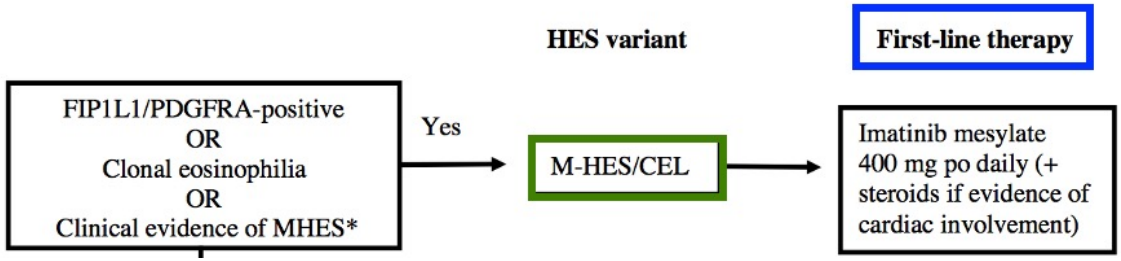
Dosage of Imatinib	n	Mean Dose	CHR	CMR
Initial dose				
400 mg/d	8	165 mg/d (n=44)	98% (42/43)	95% (18/19)
300 mg/d	1			
200 mg/d	2			
150 mg/d	1			
100 mg/d	32			
Maintenance dose				
200 mg/d	1	58 mg/d (n=29)	100% (29/29)	100% (14/14)
100 mg/d	4			
50 mg/d*	18			
<50 mg/d†	6			

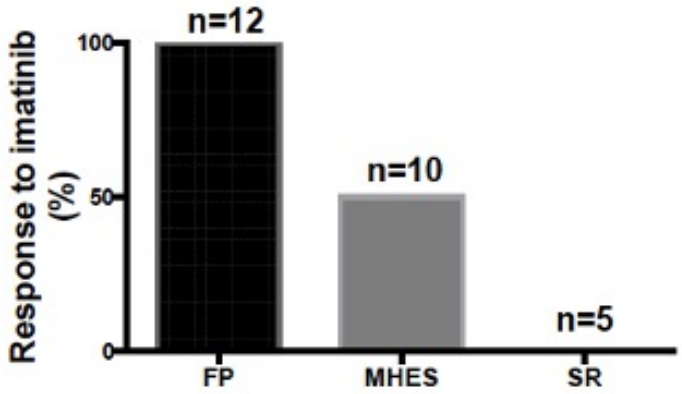
Legrand et al, Medicine 2013; 92 (5)

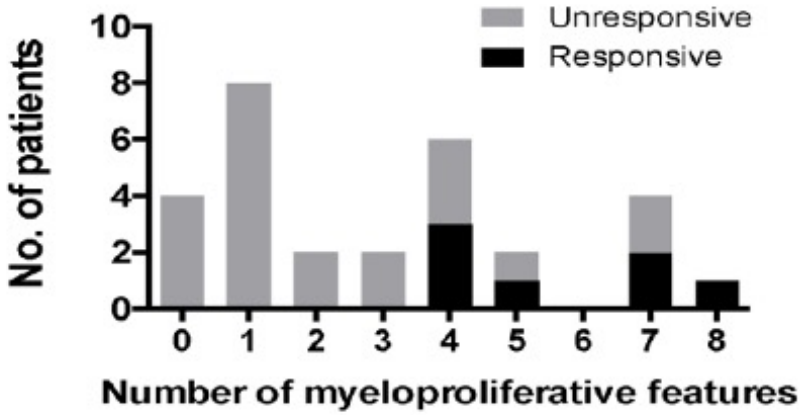
Possible « guérison » de FIP1L1-PDGFRA



En cas de suspicion clinique d'un variant myéloïde







Agents d'épargne en corticostéroïdes

Classiques:

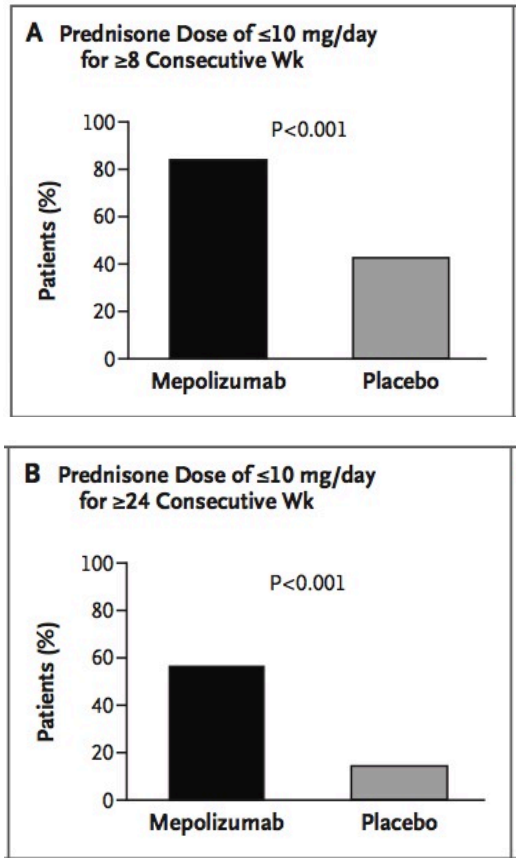
- hydroxyurée
- interferon-alpha (pégylé)

Innovants, ciblés

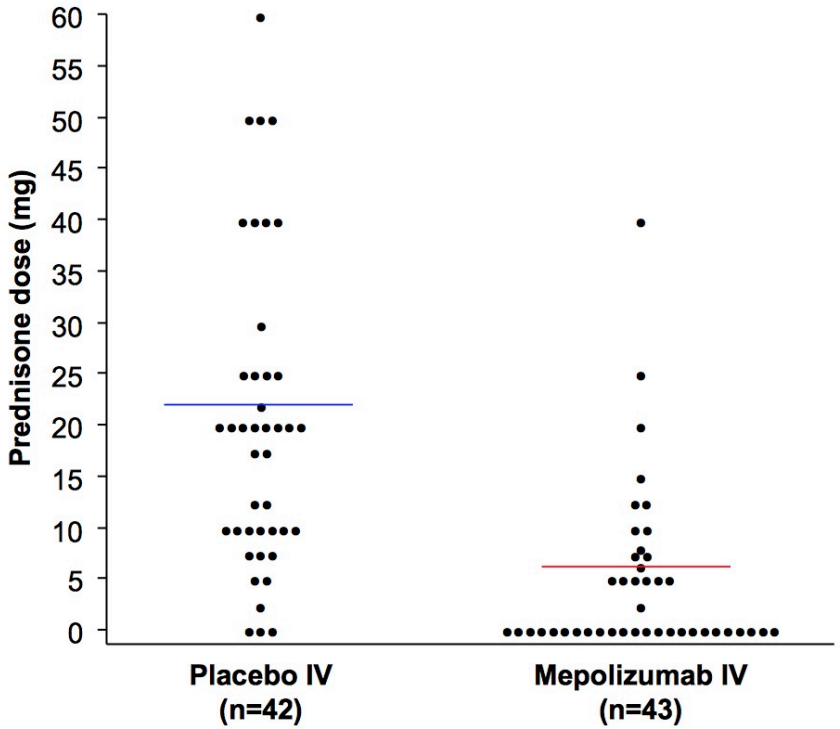
- anti-IL-5 (mepolizumab, reslizumab)
- anti-IL-5R (benralizumab)

- à l'étude: dexpramipexol, anti-siglec-8

Anti-IL-5

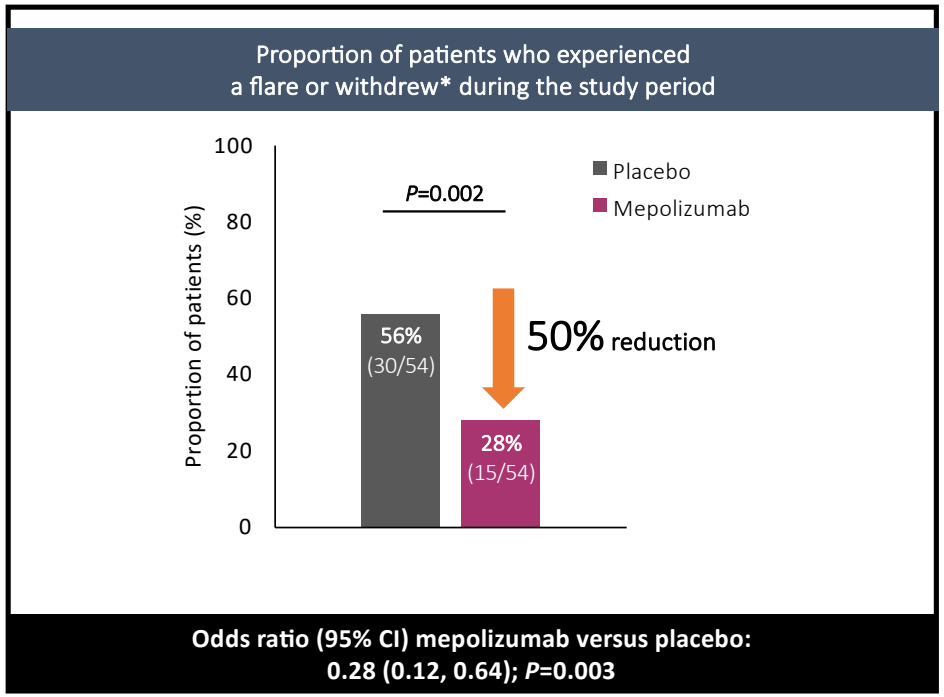


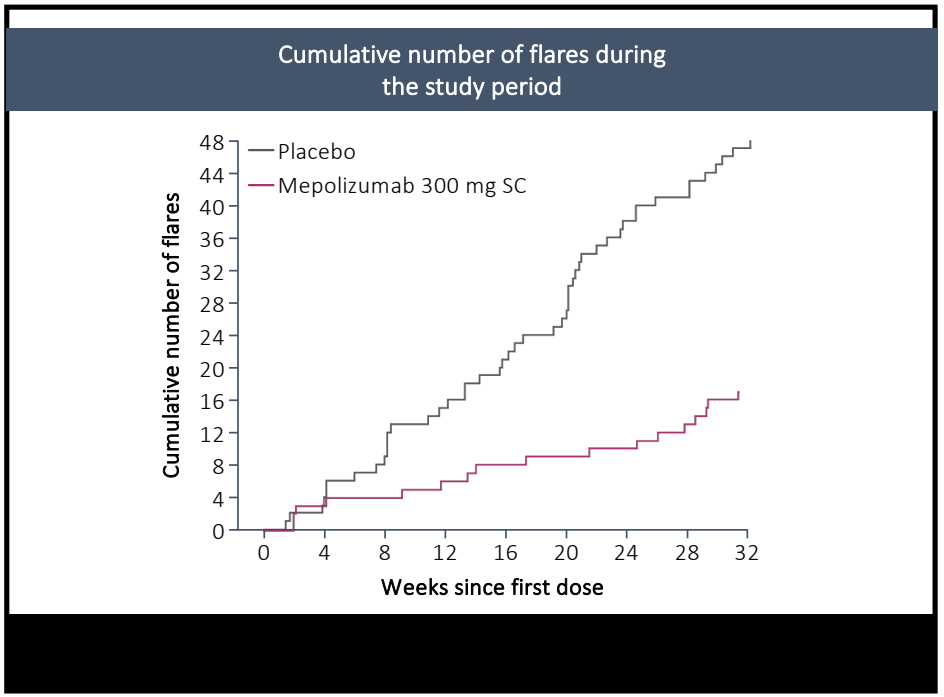
Dose PDN à la fin de l'étude



Rothenberg et al, New Engl J Med 2008; 358(12): 1215

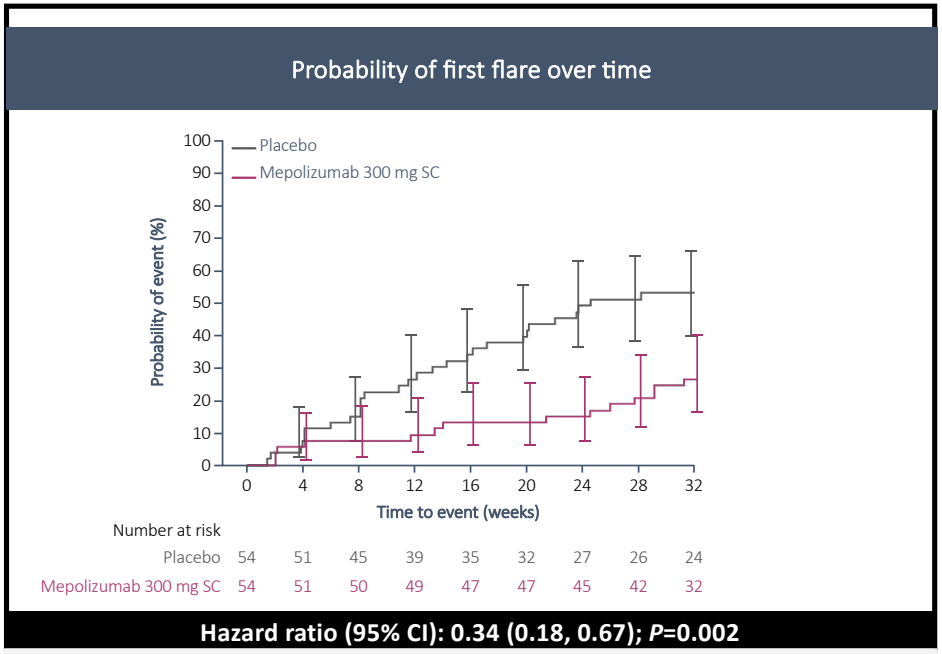
Anti-IL-5 : impact sur poussées de la maladie





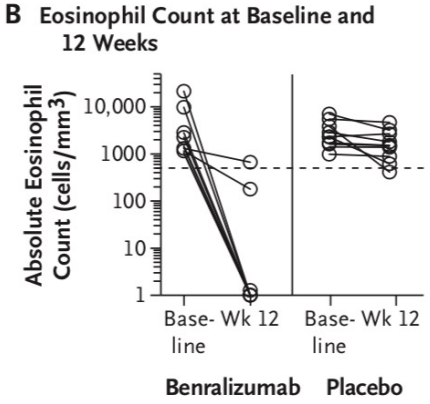
Roufosse et al, J Allergy Clin Immuol 2020;146: 1397.

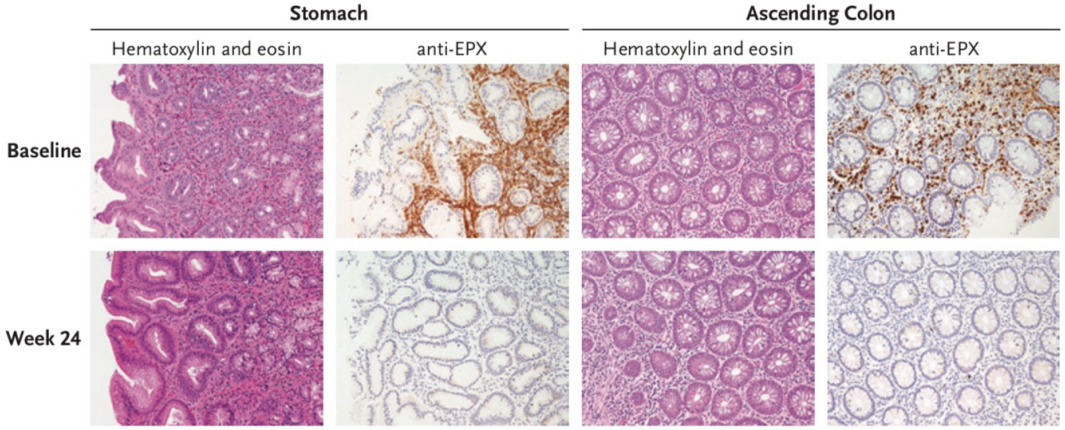
Anti-IL-5 : impact sur poussées de la maladie



Vertical bars represent 95% CI

Anti-IL-5R : étude pilote (NIH)

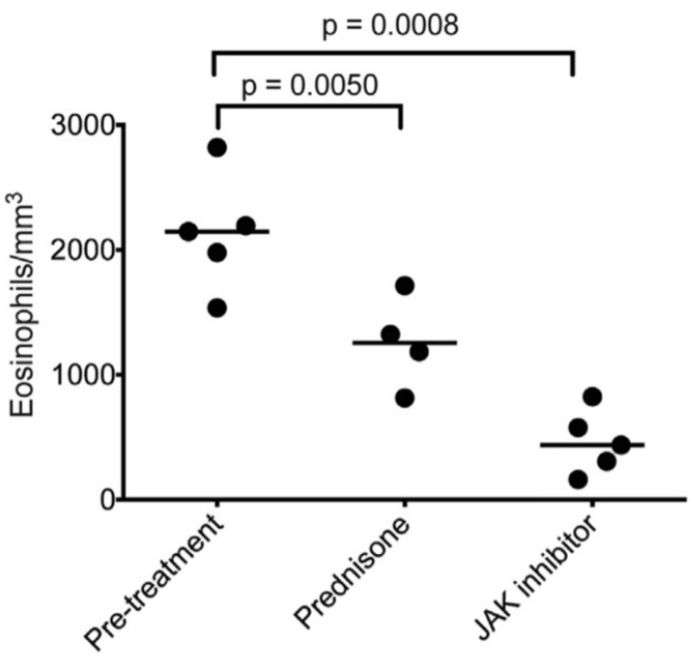


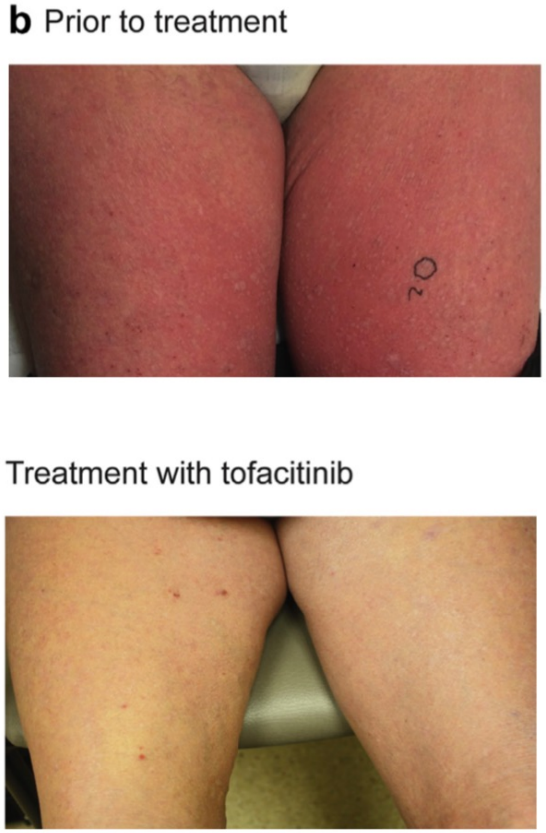


Kuang et al, NEJM 2019; 380:1336

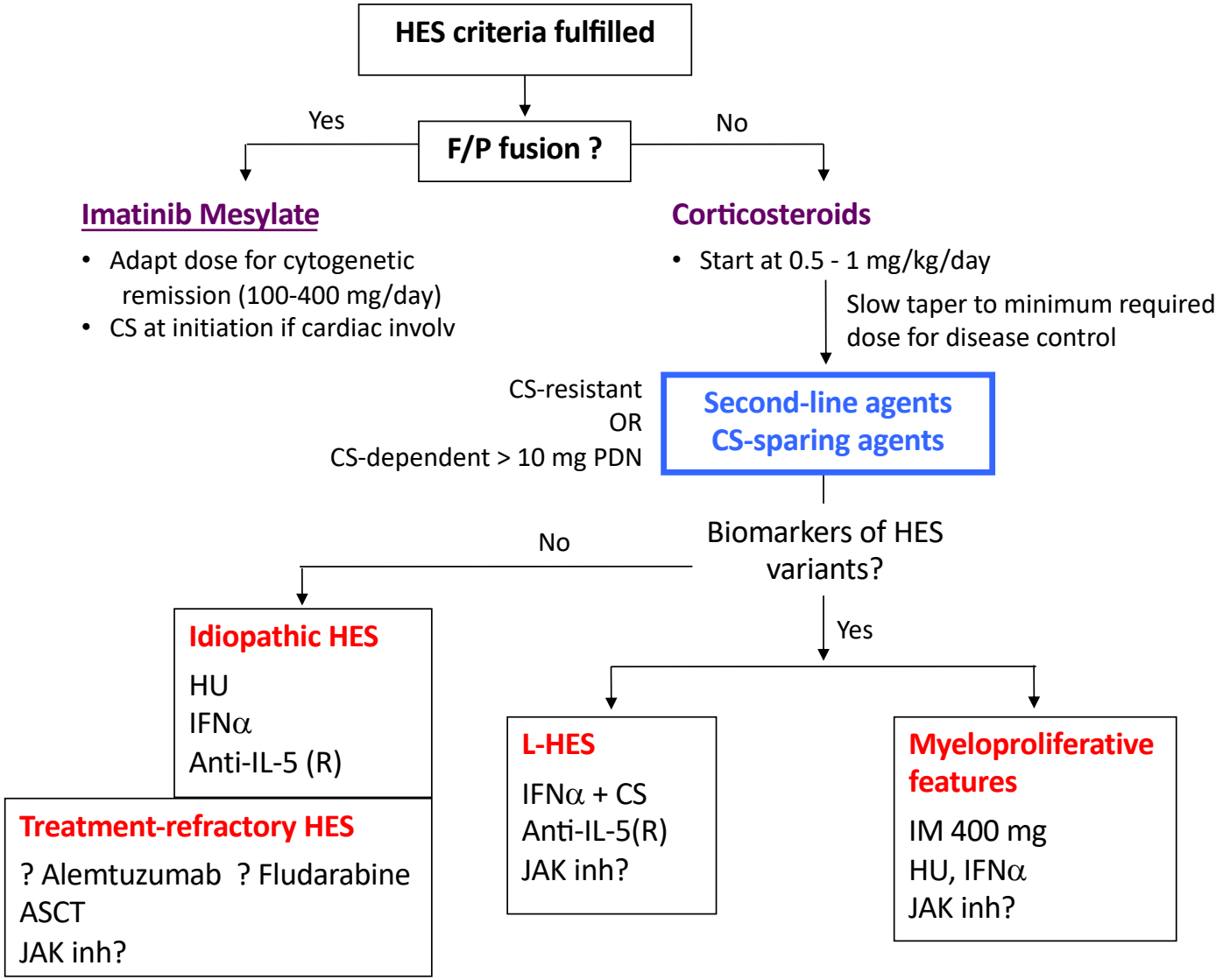
Etude clinique phase 3 en cours: NATRON

JAK inhibitors

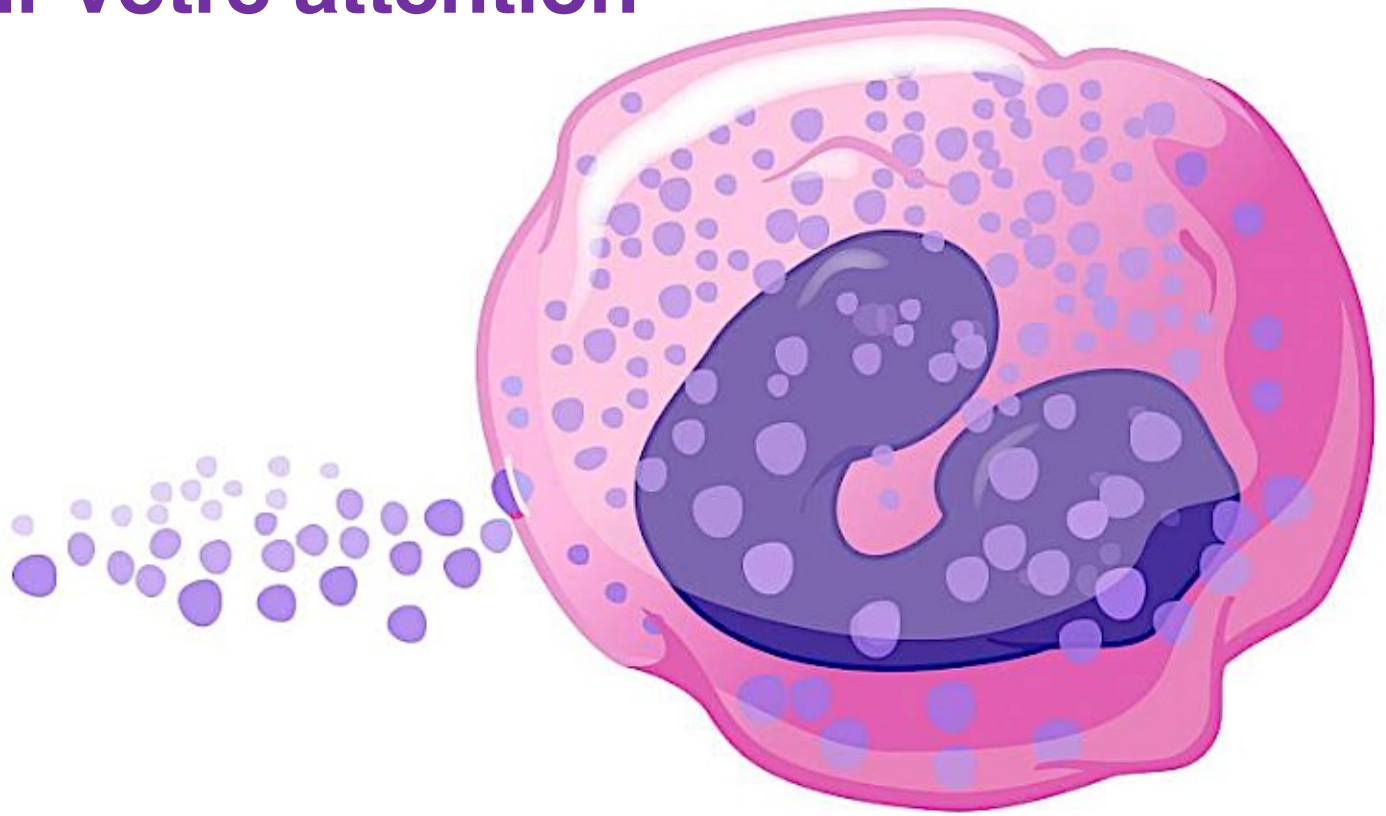




King B, et al. *J Invest Dermatol.* 2017;137:951–954.


HES criteria fulfilled
Yes
F/P fusion ?
No
Imatinib Mesylate
• Adapt dose for cytogenetic remission (100-400 mg/day)
• CS at initiation if cardiac involv
Corticosteroids
• Start at 0.5 - 1 mg/kg/day
Slow taper to minimum required dose for disease control
CS-resistant
OR
CS-dependent > 10 mg PDN
Second-line agents
CS-sparing agents
Biomarkers of HES variants?
No
Yes
Idiopathic HES
HU
IFNα
Anti-IL-5 (R)
Treatment-refractory HES
? Alemtuzumab ? Fludarabine
ASCT
JAK inh?
L-HES
IFNα + CS
Anti-IL-5(R)
JAK inh?
Myeloproliferative features
IM 400 mg
HU, IFNα
JAK inh?

Merci pour votre attention



Hyperéosinophilie de signification indéterminée

TABLE E1. Diagnosis of HE_{US}: recommended clinical and laboratory parameters*

Parameters*	Typical finding in patients with HE_{US}
Physical examination	Normal
Heart	Normal
Lungs	Clear
Liver	Normal size
Spleen	Normal size
Lymph nodes	No lymphadenopathy
Skin	No lesions, edema, or erythema
Nails	No splinter hemorrhages, nail fold infarcts
Laboratory tests	
Leukocytes	Normal or increased
Eosinophil Count	>1500 per μL blood
Basophil count†	Normal
Neutrophil count	Normal
Hemoglobin	Normal
Platelet count	Normal
Serum tryptase level	Normal
Vitamin B12 level	Normal
Troponins	Normal
Hepatic enzymes	Normal
Muscle enzymes	Normal
Renal function tests	Normal
Urinalysis	Normal
Virus serology (HIV, HTLV)	Negative
Inflammation parameters‡	Normal
Immunoglobulins	Normal
β_2-Microglobulin	Normal
Parasitology tests	Negative
Organ function parameters	
Electrocardiogram	Normal
Echocardiogram	Normal
Pulmonary function testing	Normal
Chest radiography and computed tomography	Normal (no lung infiltrates)
Abdominal ultrasound	Normal spleen size, no lymphadenopathy
Endoscopic examinations	Normal
Molecular parameters	
Immunoglobulin rearrangement	Polyclonal§
TCR rearrangement	Polyclonal§
BCR/ABL1	Negative
JAK2 V617F	Negative
KIT D816V	Negative
PDGFRA/PDGFRB rearrangements	Not found
FGFR1 rearrangements	Not found
Other molecular defects‖	Not found
BM examinations	
BM cytology	Normal except for eosinophilia
BM histology and immunohistochemistry	Normal except for eosinophilia
BM cytogenetics	Normal
BM FISH	Normal
Tissue histology (other than BM)	Normal except for eosinophilia

Hyperéosinophilie de signification indéterminée

J ALLERGY CLIN IMMUNOL
APRIL 2014

Marked and persistent eosinophilia in the absence of clinical manifestations

Yun-Yun K. Chen, BS,[a] Paneez Khoury, MD,[a] JeanAnne M. Ware, MSN, CRNP,[a] Nicole C. Holland-Thomas, MSN,[b] Jennifer L. Stoddard, BS,[c] Shakuntala Gurprasad, BS,[c] Amy J. Waldner, BA,[a] and Amy D. Klion, MD[a] *Frederick and Bethesda, Md*

Med Oncol (2014) 31:815

Characteristics and clinical outcome of patients with hypereosinophilia of undetermined significance

Grzegorz Helbig · Marek Hus · Tomasz Francuz · Joanna Dziaczkowska-Suszek · Anna Soja · Sławomira Kyrcz-Krzemień

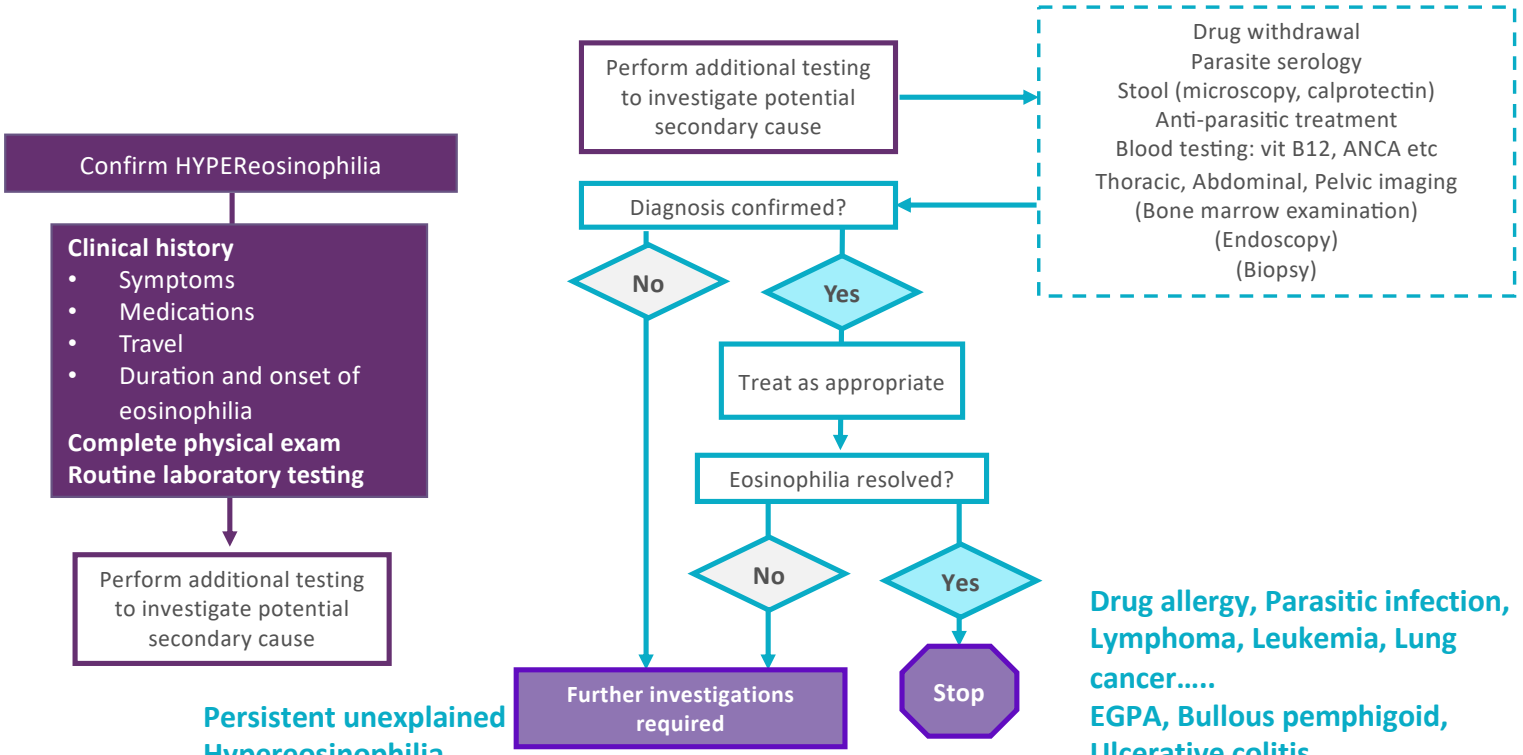
Classification des Syndromes Hyperéosinophiles

Variant
HES*
Idiopathic HES
Primary (neoplastic) HES (HES_N)
Secondary (reactive) HES (HES_R)

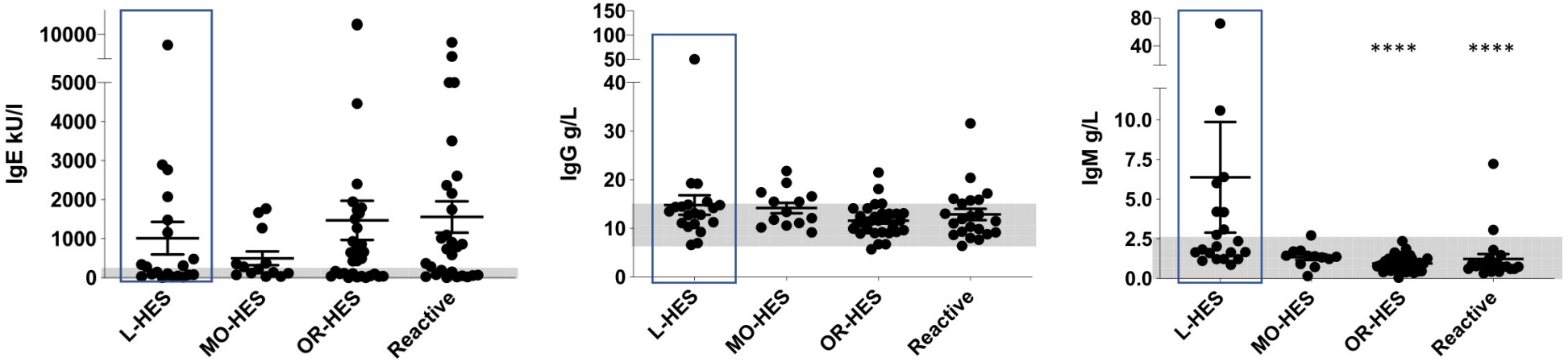
TABLE S2. Comparison of baseline characteristics between F/P+ CEL (ref 31) and CD3-CD4+ L-HES (this study) in the French Eosinophil Network

Characteristics	F/P+ CEL patients (n=44)	CD3-CD4+ L-HES patients (n=21)	p value
Age at eosinophilia onset (years)			
Median	41	39	
Range	6-67	5-75	
Sex ratio M/F (% M)	43/1 (98%)	8/13 (38%)	< 0,001
Clinical involvement			
Skin	25 (57%)	17 (81%)	0,095
Articulations / Muscles	5 (11%)	6 (29%)	
Gut tractus	7 (16%)	5 (24%)	
Lung	20 (45%)	4 (15%)	0.054
Spleen	23 (52%)	2 (10%)	< 0,001
CNS	7 (16%)	2 (10%)	
Heart, vessels	15 (34%)	1 (5%)	0.01
Eosinophilia peak (G/L)			
Median	10,1	6,1	
Range	1,9-36,9	2,2-52	
Other laboratory findings			
Anemia	16 (37%)	0	0.001
Thrombocytopenia	16 (37%)	0	0.001
TCRγδ rearrangement	8/37 (21%)	16 (76%)	< 0,001
Increased vitamin B12	28/34 (82%)	2/17 (12%)	< 0,001
Increased tryptase	21/27 (78%)	2/17 (12%)	< 0,001
Increased IgE	5/31 (16%)	18 (86%)	< 0,001
Complete remission under corticosteroids	0/14	14/18 (78%)	< 0,001

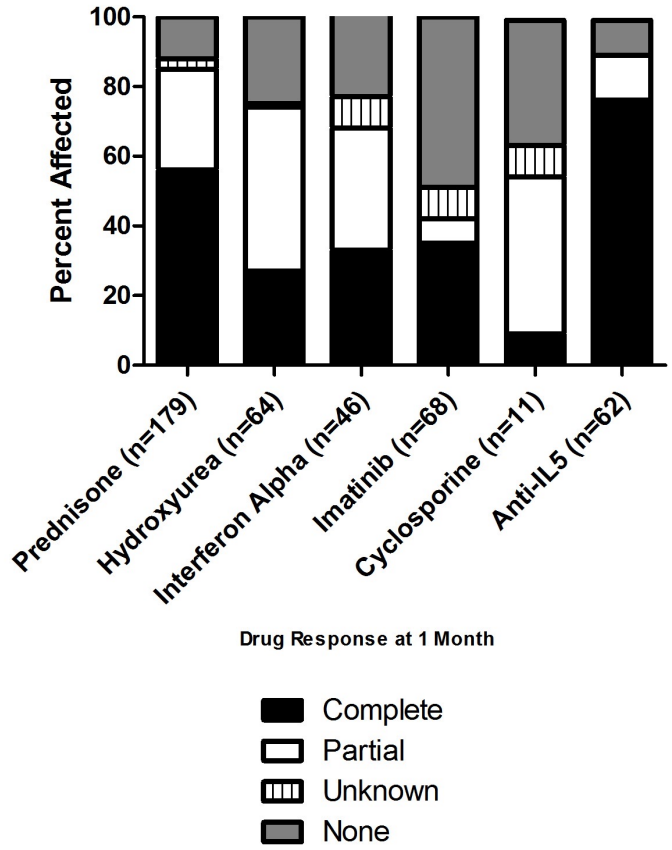
Investigation d'une HE



Les Ig sériques manquent de spécificité (sauf les IgM)



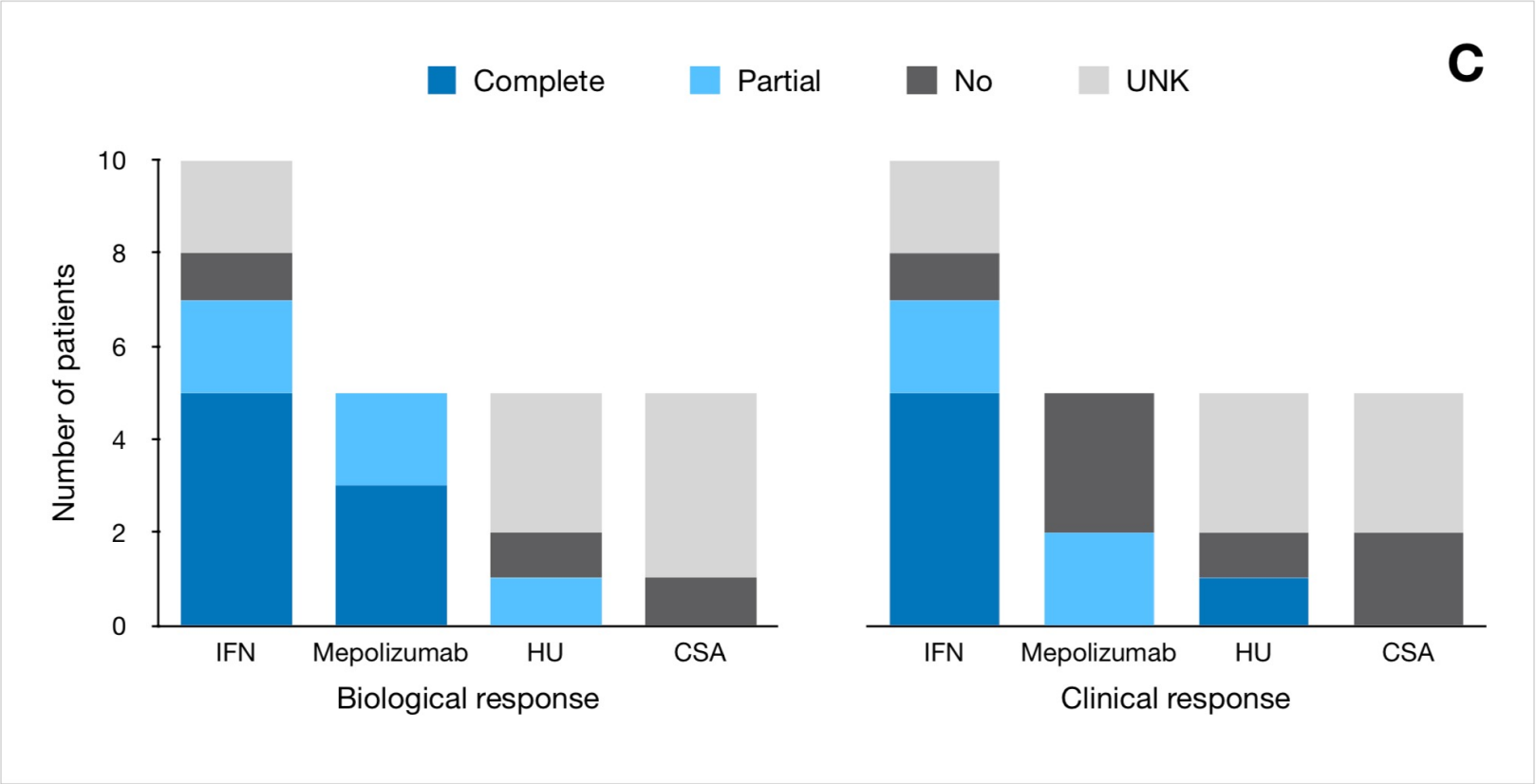
Overall response to therapy



- The majority of patients respond to corticosteroids and/or hydroxyurea
  → most commonly prescribed combination therapy
- High response rate to IFN, but poor tolerance
- Imatinib responses are observed in some patients without F/P fusion
- High response rate to mepolizumab, excellent tolerance, but not approved for HES

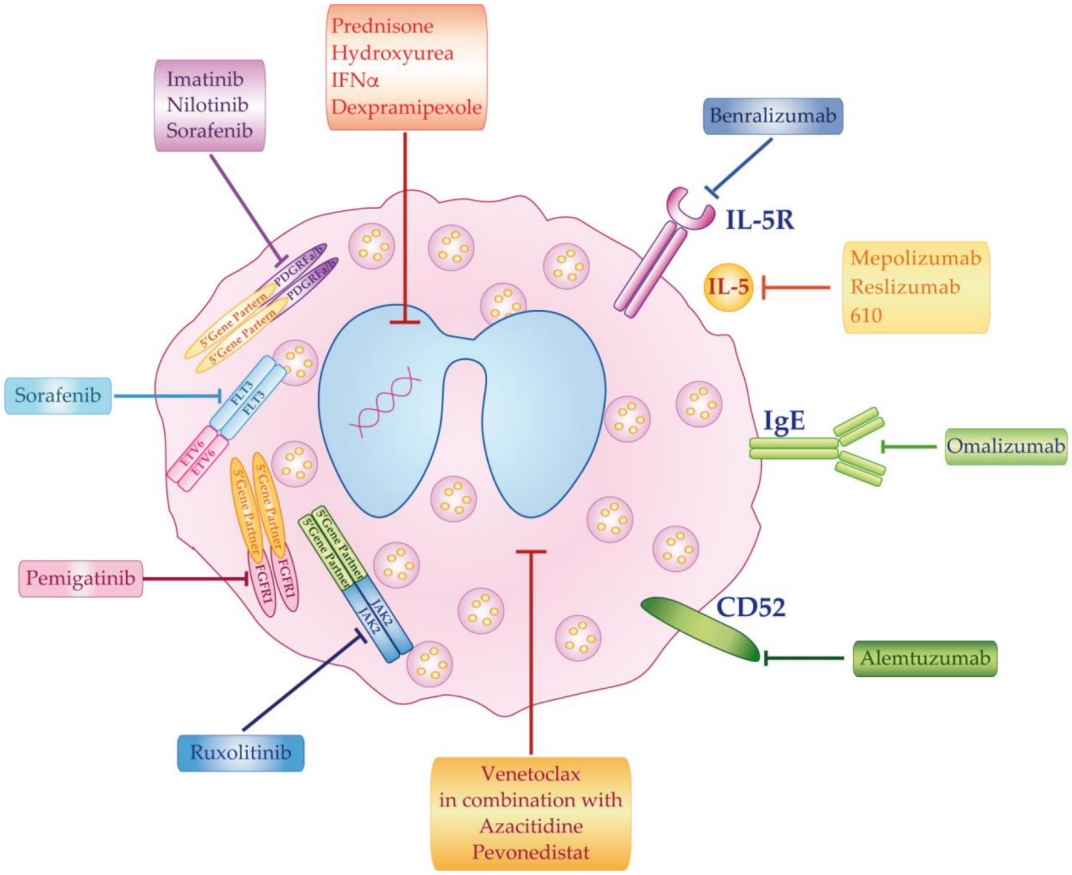
Ogbogu et al, JACI 2009; 124(6): 1319

Réponses thérapeutiques du L-HES



Carpentier et al, Front Immunol

Traitements pour les différentes variantes du HES



Int. J. Mol. Sci. **2021**, *22*, 486