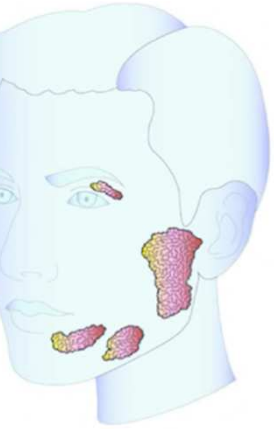
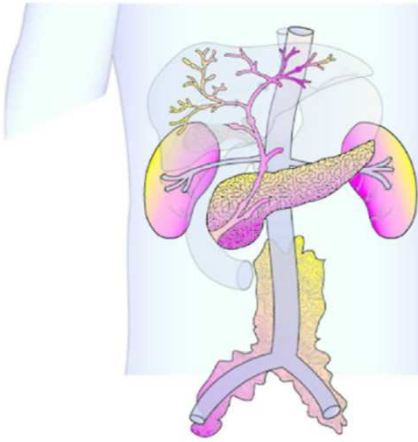




Maladie associée aux IgG4

Mikael Ebbo

Département de Médecine Interne, hôpital de la Timone, AP-HM

Nathalie Costedoat-Chalumeau

ix*Marseille université Initiative d'excellence

Ciml IMMUNOLOGY

Assistance Publique Hôpitaux de Marseille

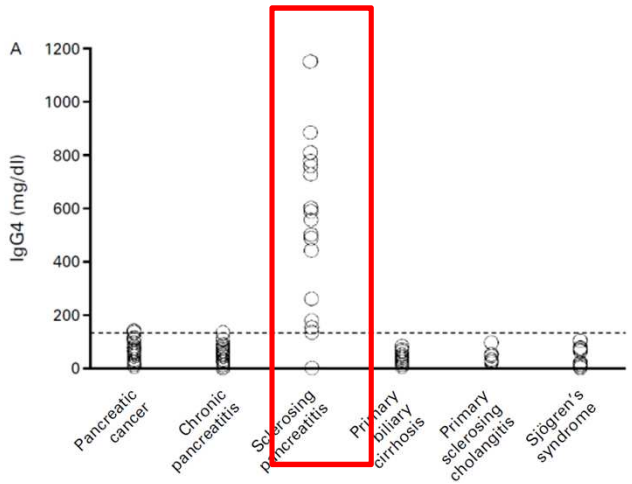
MARSEILLE IMMUNOPÔLE

Le concept de « maladie associée aux IgG4 »

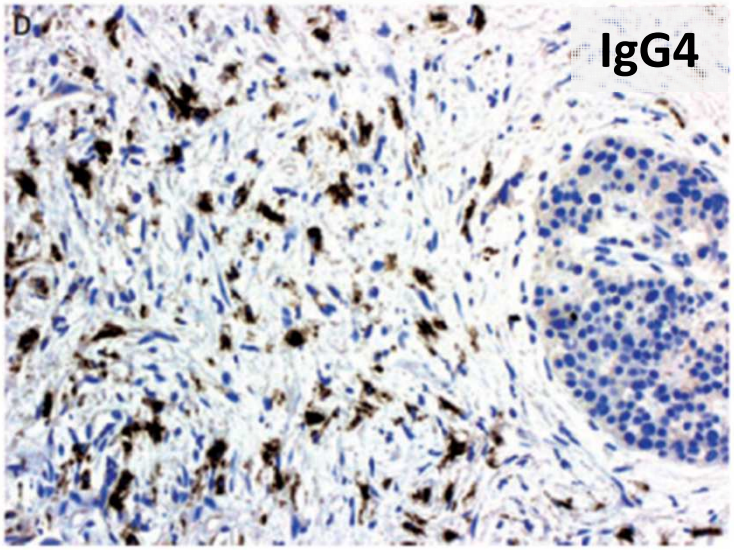
The New England Journal of Medicine

HIGH SERUM IgG4 CONCENTRATIONS IN PATIENTS WITH SCLEROSING PANCREATITIS

AMANO, M.D., SHIGEYUKI KAWA, M.D., AKIRA HORIUCHI, M.D., HIROSHI UNNO, M.D., NAOYUKI FURUYA, M.D., TAIJI AKAMATSU, M.D., MANA FUKUSHIMA, M.D., TOSHIO NIKAIDO, PH.D., KOHZO NAKAYAMA, PH.D., NOBUTERU USUDA, M.D., AND KENDO KIYOSAWA, M.D.



2003



2012

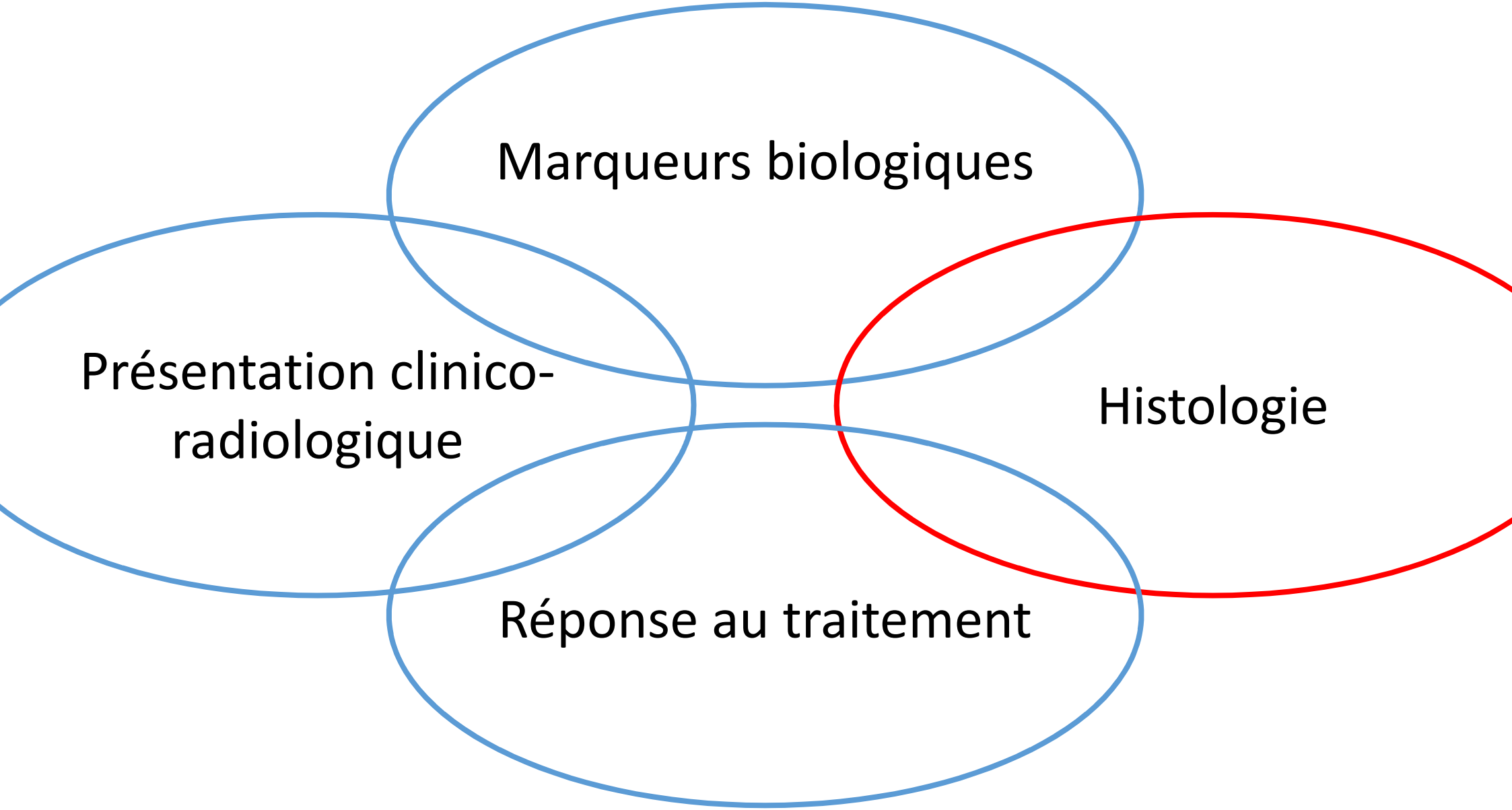
SPECIAL ARTICLE

Recommendations for the Nomenclature of IgG4-Related Disease and Its Individual Organ System Manifestations

Stone JH et al. A&R

Diagnostic

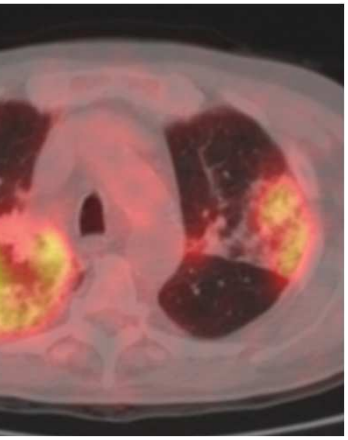
Comment retenir un diagnostic de MAG4 ?

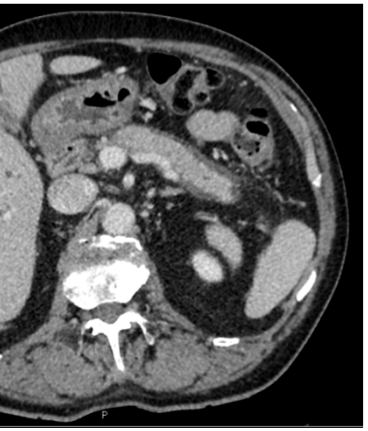


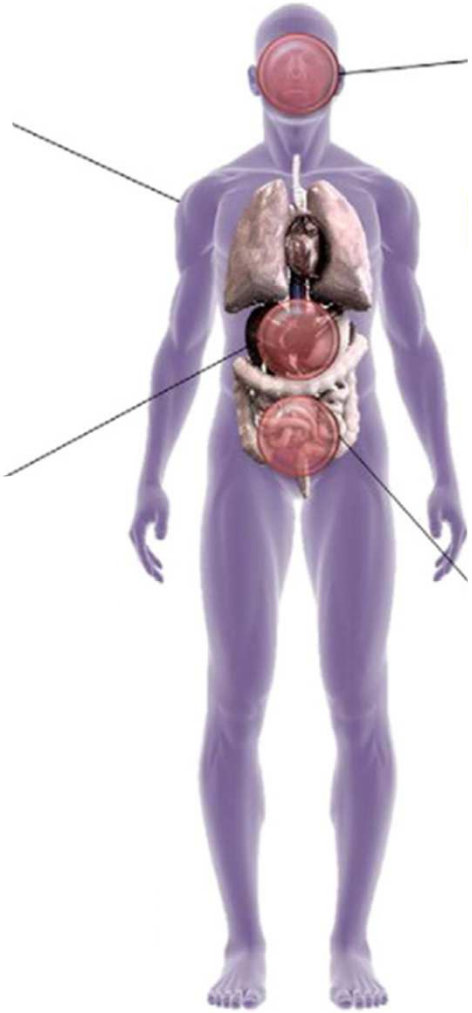
Comment retenir un diagnostic de MAG4 ?

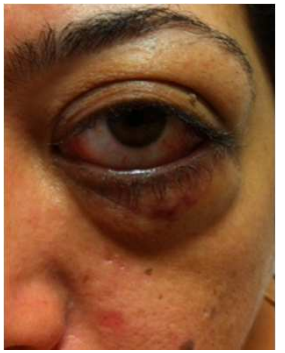
Présentation clinico-radiologique

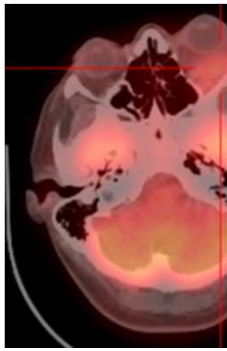
« Maladie associée aux IgG4 »: atteintes d'organes

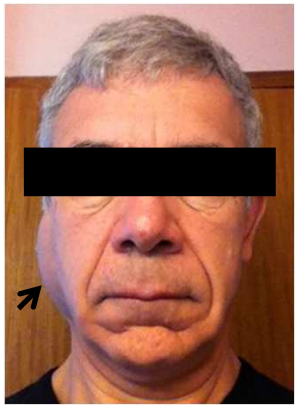


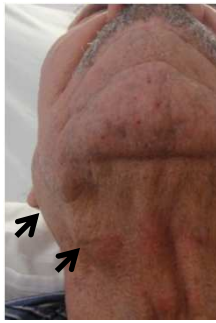


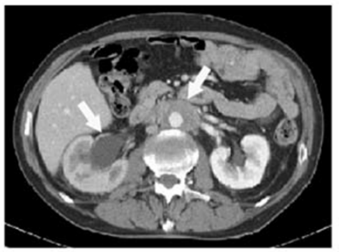


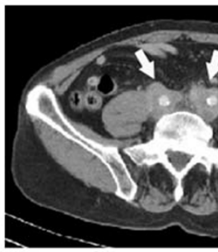










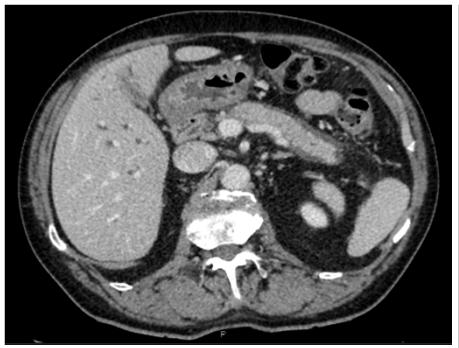


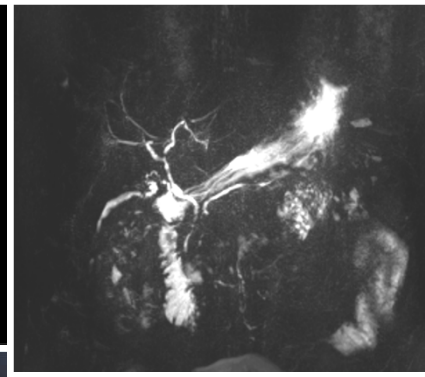
Frequencies of the main organ involvements obtained in series including unselected cases of IgG4-RD (systemic series).

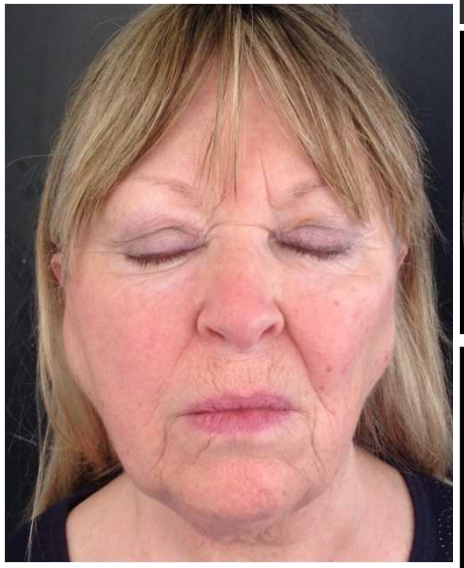
P. Brito-Zerón et al. / Autoimmunity Reviews 13 (2014) 12

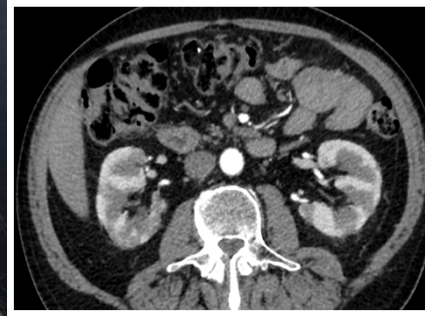
qui est fréquent et évocateur

	Grados et al.[15]	Wallace et al.[13]	Fernandez-Codina A et al.[19]	Campochiaro et al.[16]	Chen H et al.[17]	Lin W et al.[18]	Inoue D et al.[14]*
tients	90	125	55	41	28	118	235
creas	**44**	19	16	44	32	38	60
rgan	81	62	47	58	86	78 (>2)	58
rgans	36	38	-		42		
ry tree	**27**	9	4	10	29	17	13
r	-	2	-	-	-	-	-
ph nodes	**58**	27	2	12	43	65	14
vary gland	**32**	28	16	19	79	64	34
yoadenitis	9	-	22	-	46	50	23
t	7	22	15	7	4	-	4
ney	**32**	12	7	2	11	24	9
	28	18	27	19	11	26	4
g	14	17	9	2	4	27	5
	30	-	-	-	11	8	-
a	13	11	9	10	4	0	20
inges	2	2	4	7	-	0	-
	-	2	0	0	-	4	-
sitis	-	4	-	4	4	12	-
entery	1	2	7	-	-	0	-
tate	6	3	-	-	14	35	-
iastinitis	0	2	-	-	7	3	-
oid	1	-	-	-	-	1	-









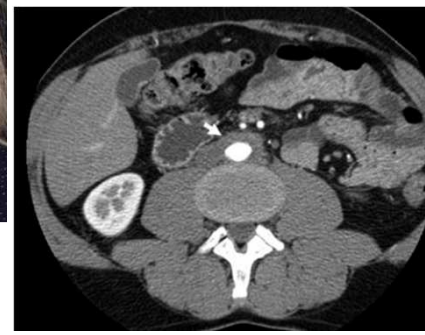
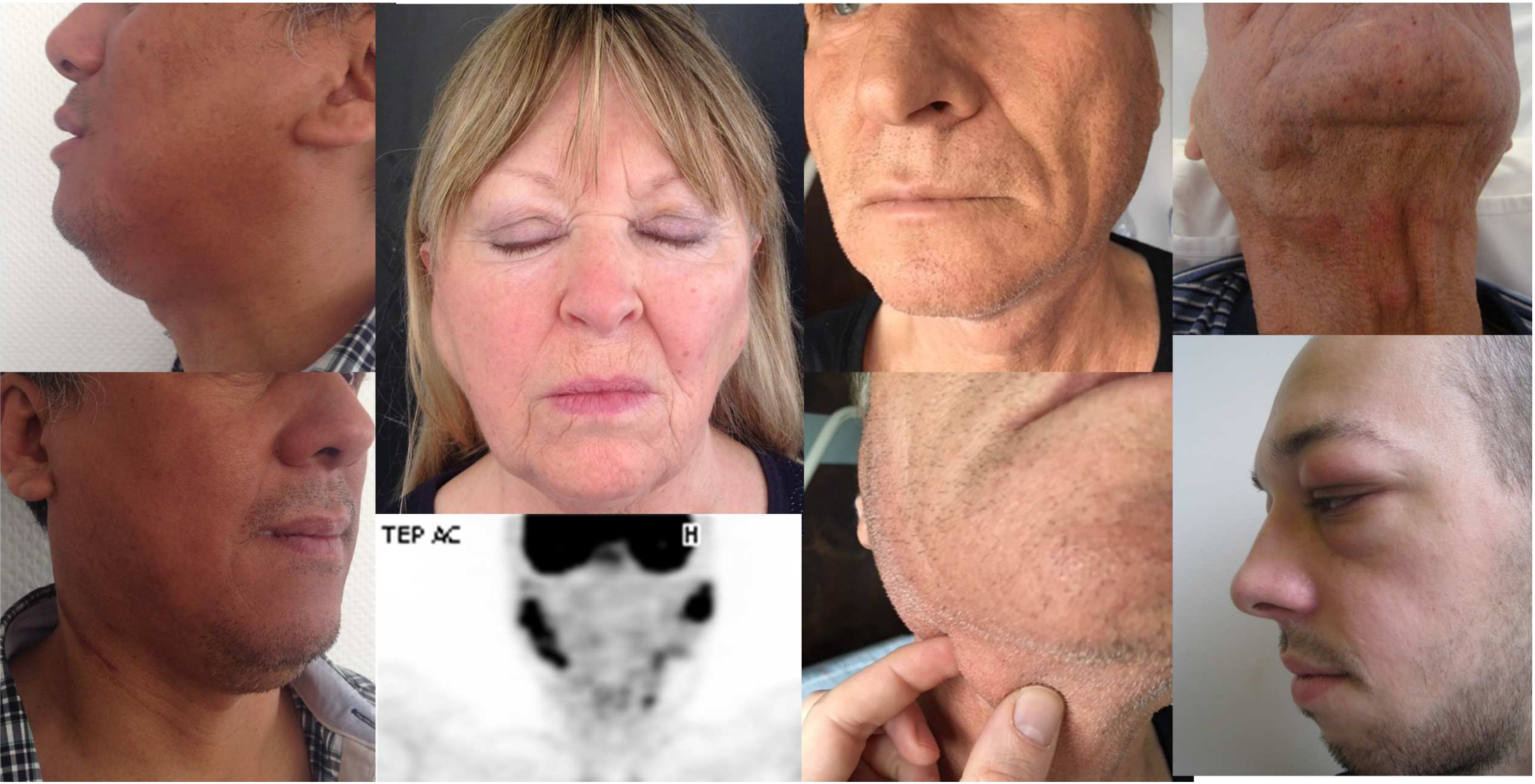
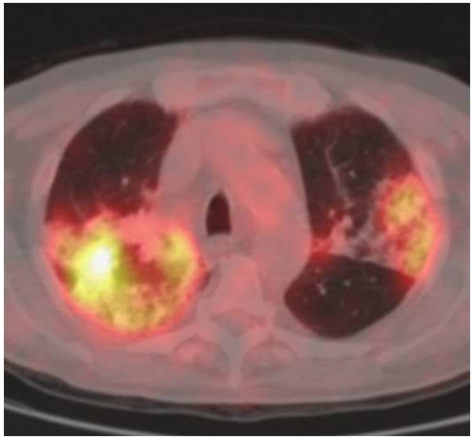
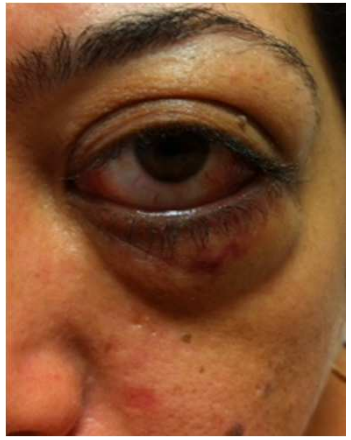
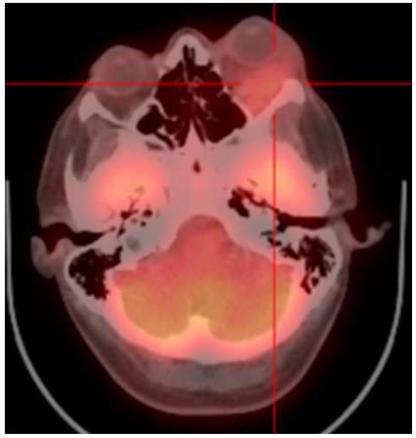
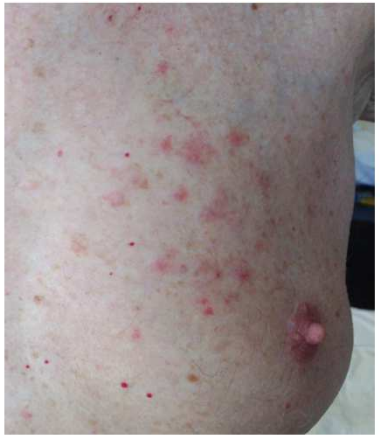
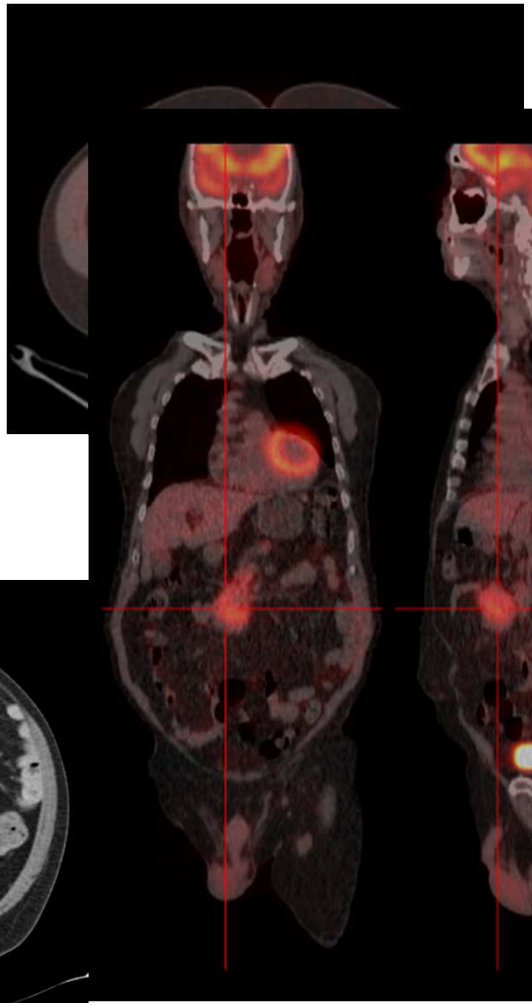
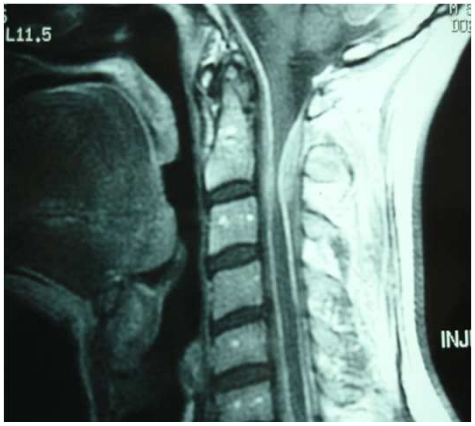


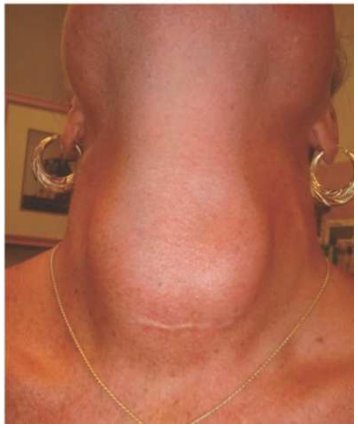
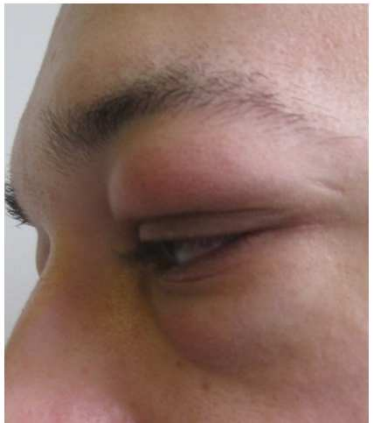
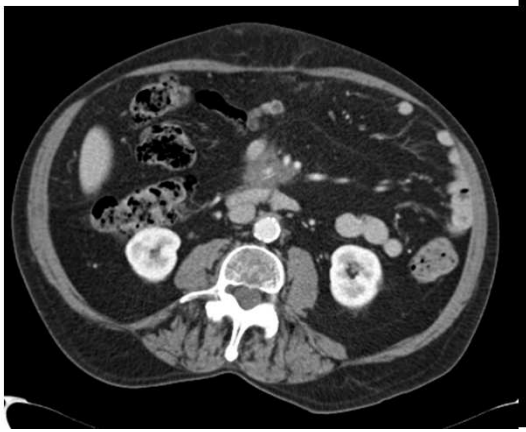
Table I. Frequency (in %) of organ involvements in case series of IgG4-RD. *Schleinitz N. et al. In Fibroinflammatory disorders. Springer. Vaglio A*

Atteinte des glandes salivaires
(parotidomégalie, Sd de Mikulicz, tumeur de Küttner…)

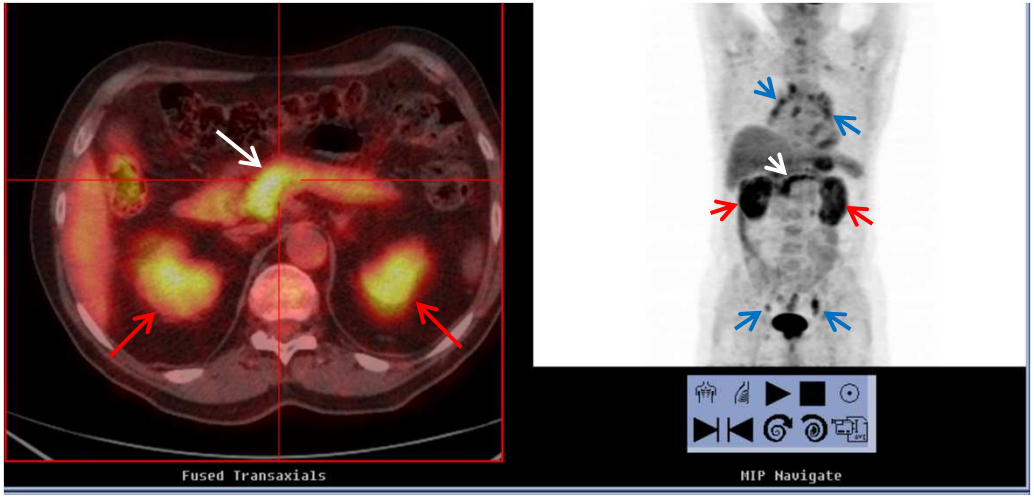


Ce qui est plus rare…

Intérêt du TEP au cours de l'IgG4-RD



n=21
46 TEP-TDM

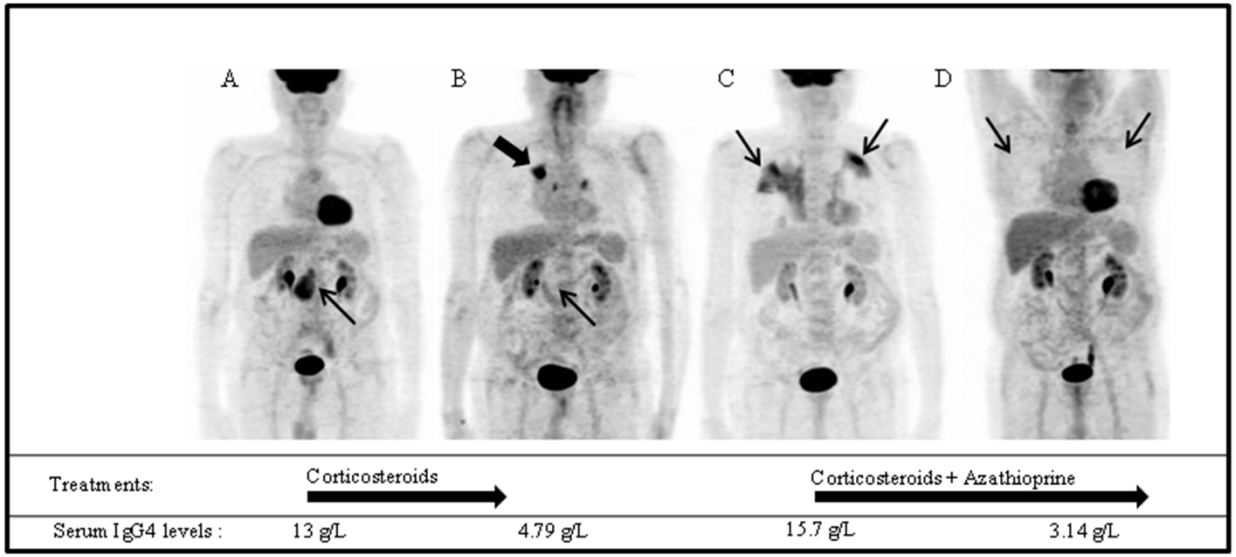
+ Sb que l'imagerie conventionelle dans 65% des cas (Aorte, glds salivaires, ADP)

Qq faux – (petite taille, cerveau/reins)

=> Intérêt Δ^{ic} + orientation biopsies

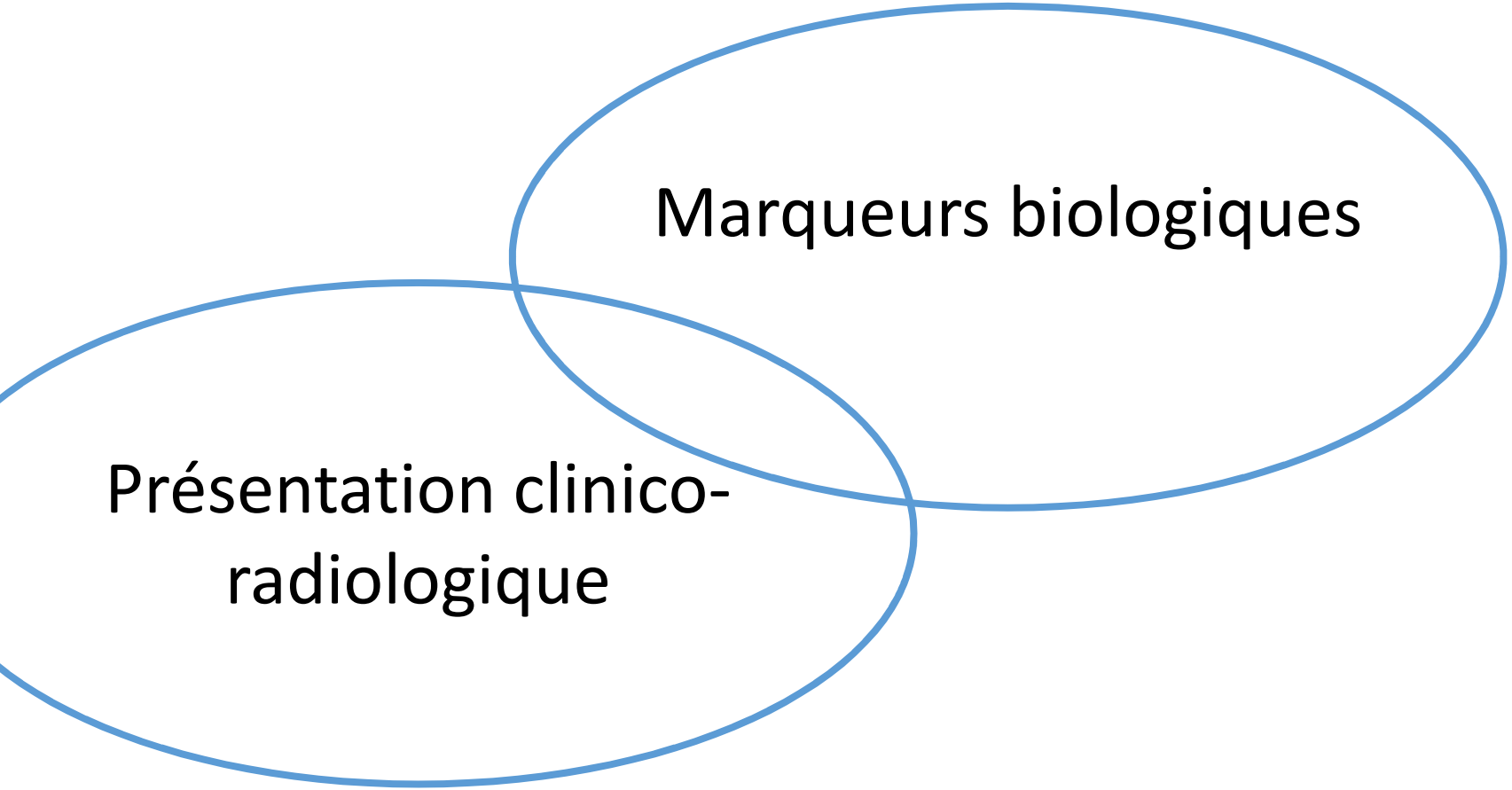
Bonne corrélation avec réponse clinico-biologique au traitement

Intérêt dans le suivi
Et dépistage des rechutes ?



Ebbo et al, *Arthritis Care & Research 2014*

Comment retenir un diagnostic de MAG4 ?



« Maladie associée aux IgG4 »: Critères de classification / diagnostiques

2

Comprehensive Clinical Diagnostic (CDC) Criteria

xamen clinique : hypertrophie localisée ou diffuse au sein d'un ou de plusieurs organes siquement atteints au cours de la MAG4.
iologie : élévation des IgG4 sériques (≥135 mg/dl ou 1,35 g/l).
istologie montrant : nfiltration lymphocytaire et plasmocytaire polyclonale marquée + fibrose nfiltration par des plasmocytes IgG4+ : ratio plasmo IgG4+/IgG+>40% et >10 plasmo IgG4+/CFG
G4 définie= 1) + 2) + 3) G4 probable= 1) + 3) G4 possible= 1) + 2)
endant, il faudra dans tous les cas éliminer, en particulier au niveau histologique, les principaux nostics différentiels de MAG4 : tumeur maligne au sein du/des organes atteints (cancer, phome), et tableaux cliniques proches : syndrome de Gougerot-Sjögren, cholangite sclérosante nitive, maladie de Castleman, fibrose rétro-péritonéale secondaire, granulomatose de Wegener, oïdose, syndrome de Churg et Strauss.

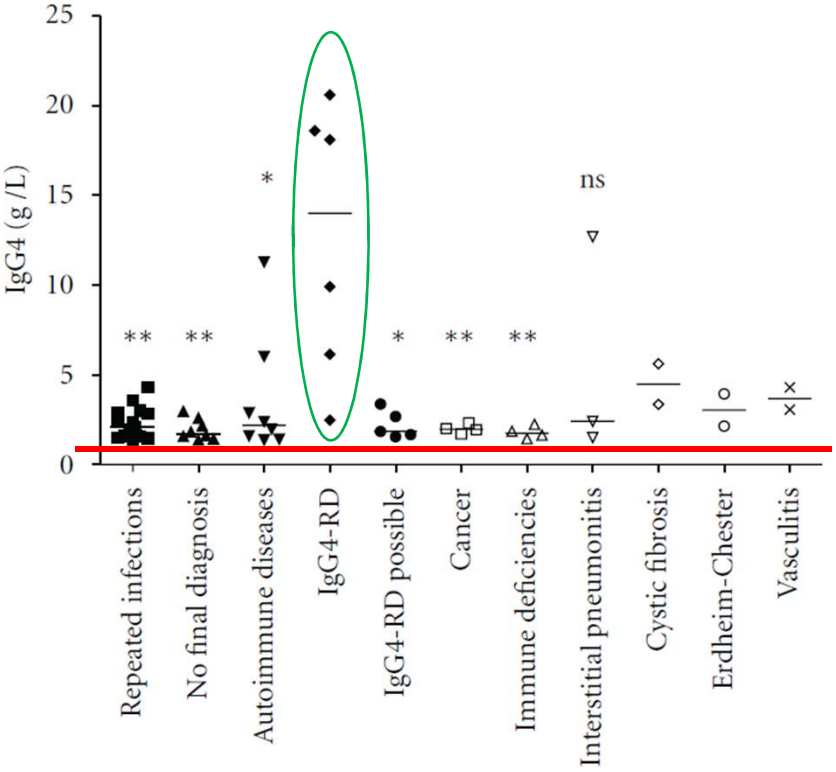
Un diagnostic d'exclusion !!!

Umehara et al. Modern Rheumatol 2012

Attention au « sur-diagnostic »!

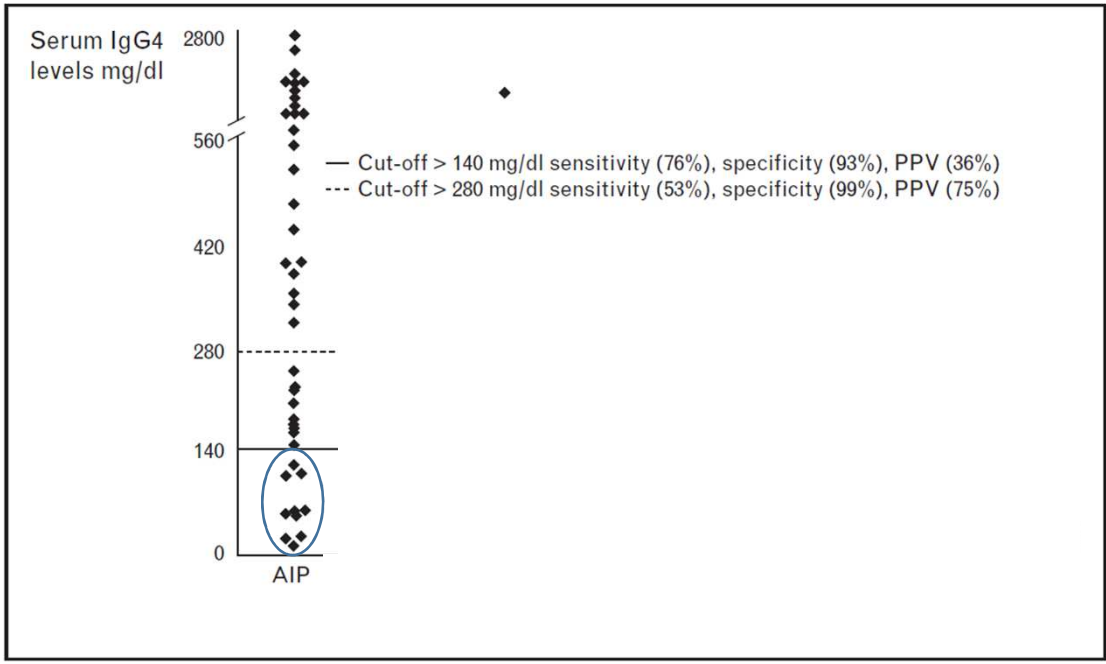
Elévation des IgG4 sériques

Un marqueur non spécifique...



Ebbo et al. *Int J Rheumatol* 2012

... et absent chez près de 30% des patients!



Sah RP, Chari ST. *Curr Opin Rheumatol* 2011

Corrélée à la réponse au traitement?
Corrélée au risque de rechute?

⇒ Nécessité d'identifier de nouveaux biomarqueu
A visée diagnostique + pour le suivi

Les autres marqueurs biologiques (non spécifiques)

Hyper-gammaglobulinémie polyclonale : le + souvent (73% des cas)

Syndrome inflammatoire biologique : possible (47% des cas), mais modéré

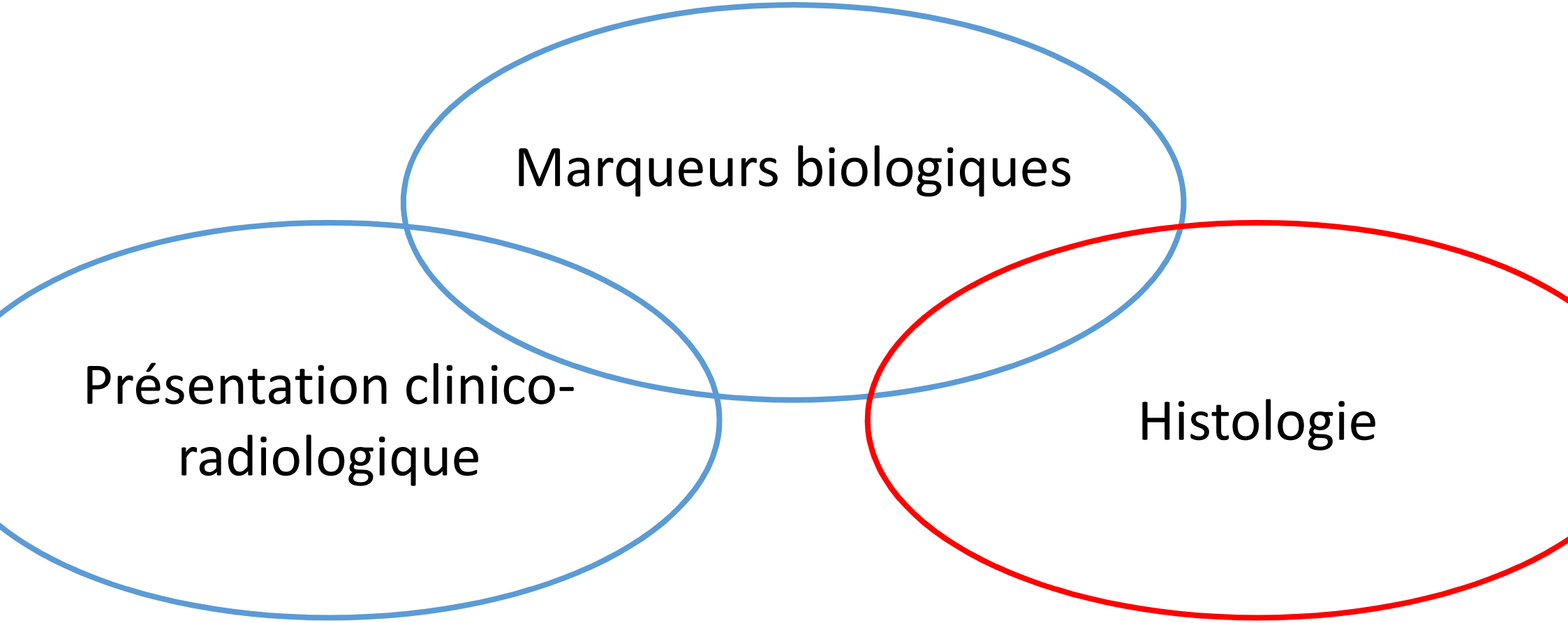
Hyperéosinophilie / hyper-IgE : possibles (1/3), parfois marquée

Marqueurs d'auto-immunité : possible (25% Ac Anti-nucléaires +)
mais à faibles taux et non spécifiques (anti-SSA et anti-SSB toujours négatifs)

Consommation du complément : certains patients (30% des cas)
Patients avec présentation systémique et atteinte rénale ++

Ebbo et al, *Medicine (Baltimore)* 2012; Cohorte nationale de la maladie associée a

Comment retenir un diagnostic de MAG4 ?



Le concept de « maladie associée aux IgG4 »

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Un diagnostic d'exclusion !!!

Consensus statement on the patholog
IgG4-related disease
MODERN PATHOLOGY

Umehara et al. Modern Rheumatol 2012

Le concept de « maladie associée aux IgG4 »

us statement on the pathology of IgG4-related disease

nde *et al* MODERN PATHOLOGY (2012) 25, 1181–1192

Characteristic histological features
1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, usually storiform in character
3. Obliterative phlebitis

Cases with ≥ 2 pathology features

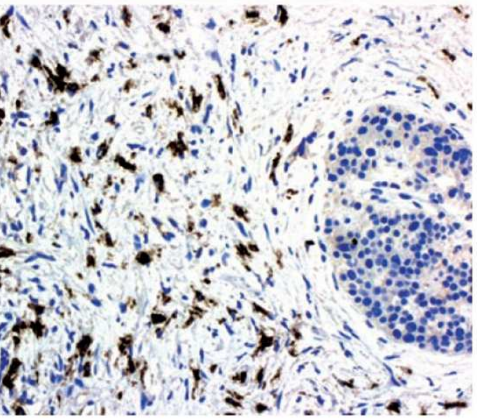
Cases with 1 pathology feature

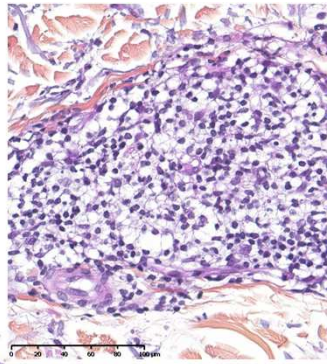
	Numbers of IgG4+ plasma cells (/hpf)		Ref
Meningus	>10	>10	55
Lacrimal gland	>100	>100	28
Salivary gland	>100	>100	17,34
Lymph node	>100	>50	27
Lung (surgical specimen)	>50	>50	10,35
Lung (biopsy)	>20	>20	10,35
Pleura	>50	>50	
Pancreas (surgical specimen)	>50	>50	
Pancreas (biopsy)	>10	>10	
Bile duct (surgical specimen)	>50	>50	
Bile duct (biopsy)	>10	>10	
Liver (surgical specimen)	>50	>50	
Liver (biopsy)	>10	>10	
Kidney (surgical specimen)	>30	>30	
Kidney (biopsy)	>10	>10	
Aorta	>50	>50	
Retroperitoneum	>30	>30	
Skin	>200	>200	

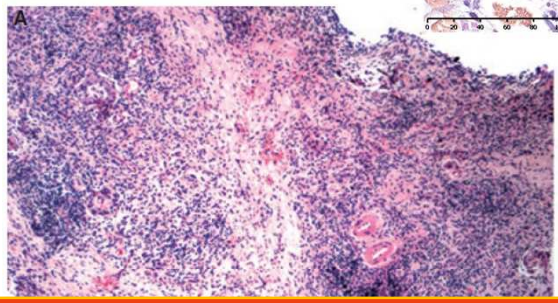
IgG4+/IgG+ plasma cell ration >40% a mandatory for histological diagnosis of IgG4-RD

Green boxes = Histologically highly suggestive of IgG4-RD

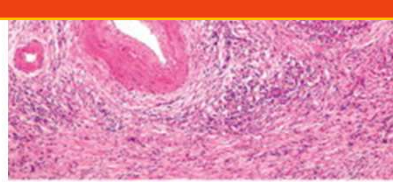
Orange boxes = Probable histological features of IgG4-RD



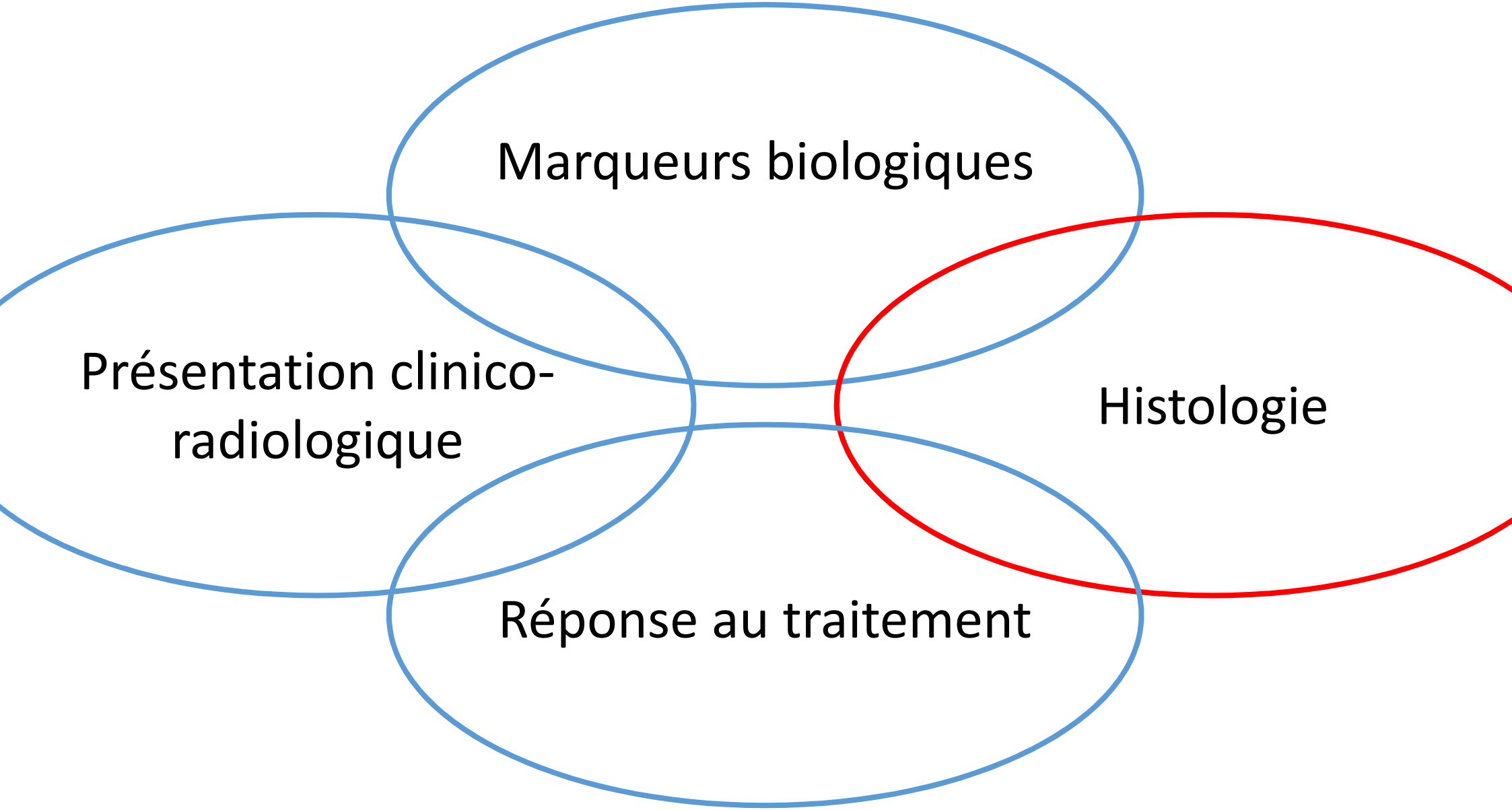




Pas de nécrose
Pas de vascularite
Pas de granulome
Pas de prédominance de PNN/histiocy
Pas de monoclonalité



Comment retenir un diagnostic de MAG4 ?



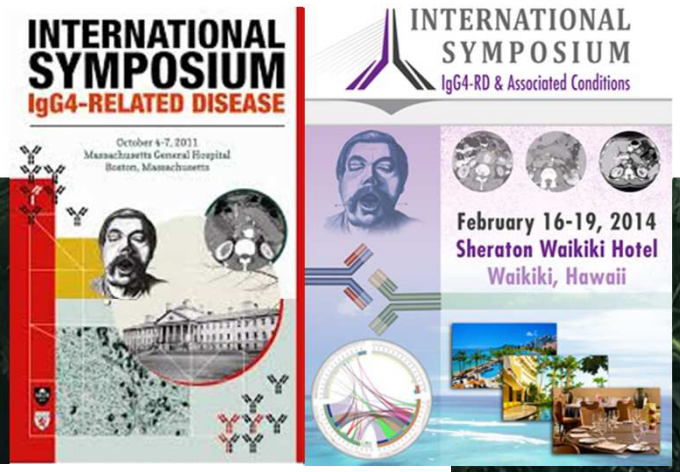
Nouveaux critères de classification

Vers de futurs critères de classification de l'ACR/EULAR 2018-201

500 x2

ients IgG4-RD

« Mimickers »



Validations de critères de **classification**

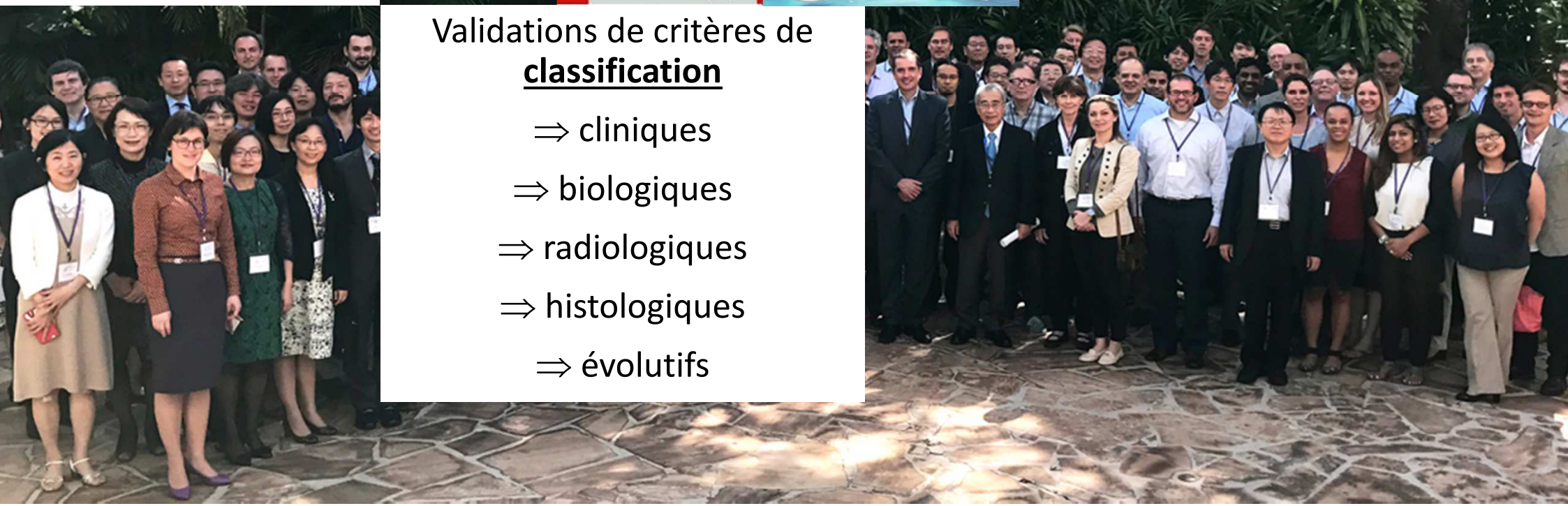
⇒ cliniques

⇒ biologiques

⇒ radiologiques

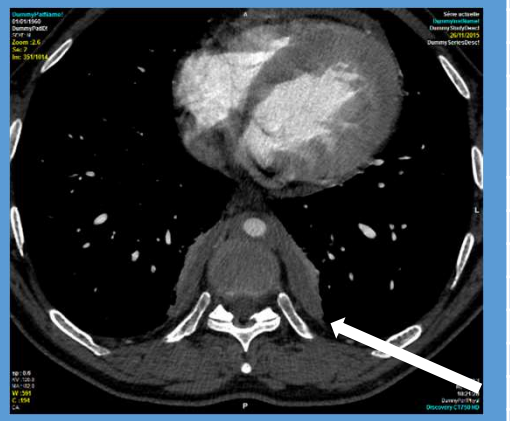
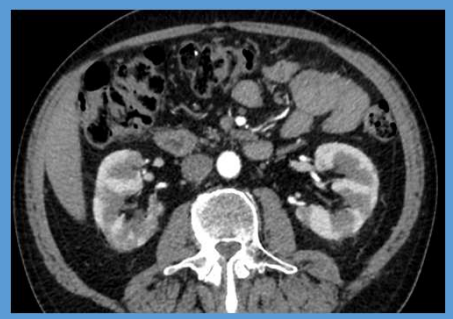
⇒ histologiques

⇒ évolutifs



ia	Characteristic* clinical or radiologic involvement of a typical organ (e.g., pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges)	Yes or No**
riteria	Domains and Items	
	Clinical	Yes or No***
	Fever	
	No objective response to glucocorticoids	
	Serological	
	Leukopenia and thrombocytopenia with no explanation	
	Peripheral eosinophilia	
	ANCA positive (specifically against proteinase 3 or myeloperoxidase)	
	Positive SS-A (Ro) or SS-B (La) Antibody	
	Positive dsDNA, ribonucleoprotein, or Smith (Sm) Antibody	
	Other disease-specific auto-antibody	
	Cryoglobulinemia	
	Radiology	
	Known radiologic findings suspicious for malignancy or infection that have not been sufficiently investigated	
	Rapid radiologic progression	
	Long bone abnormalities consistent with Erdheim-Chester disease	
	Splenomegaly	
	Pathology	
	Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated	
	Markers consistent with inflammatory myofibroblastic tumor	
	Prominent neutrophilic inflammation	
	Necrotizing vasculitis	
	Prominent necrosis	
	Primary granulomatous inflammation	
	Pathologic features of macrophage/histiocytic disorder	
	Known Diagnoses of the Following	
	Multicentric Castleman's Disease	
	Crohn's disease or Ulcerative Colitis (if only hepatopancreatobiliary disease is present)	
	Hashimoto's thyroiditis (if only the thyroid is affected)	

If case meets entry criteria and does not meet any exclusion criteria, proceed to step 3.

3. Inclusion Criteria	*Domains and Items*
	**Histopathology**
	Uninformative biopsy
	Dense Lymphoplasmacytic Infiltrate
	Dense Lymphoplasmacytic Infiltrate and Obliterative Phleb
	Dense Lymphoplasmacytic Infiltrate and Storiform Fibrosis with or without Obliterative Phlebitis
	Immunostaining† (Table 4)
	Serum IgG4 Concentration
	Normal or Not Checked
	> Normal but < 2x Upper Limit of Normal
	2x to 5x Upper Limit of Normal
	≥ 5x Upper Limit of Normal
	**Bilateral Lacrimal, Parotid, Sublingual, and Submandibular Glands**
	No set of glands is involved
	One set of glands is involved
	Two or more sets of glands are involved
	Chest and Thoracic Aorta
	Neither of the items listed is present
	Peribronchovascular and septal thickening
	Paravertebral Band-Like Soft Tissue in the Thorax
	Pancreas and Biliary Tree
	None of the items listed is present
	Diffuse pancreas enlargement (loss of lobulations)
	Diffuse pancreas enlargement and capsule-like rim with decreased enhancement
	Pancreas (either of above) and biliary tree involvement
	Kidney
	None of the items listed is present
	Hypocomplementemia
	Renal pelvis thickening/soft tissue
	Bilateral renal cortex low density areas
	Retroperitoneum
	Neither of the items listed is present
	Diffuse thickening of the abdominal aortic wall
	Circumferential or antero-lateral soft tissue around the inf renal aorta or iliac arteries
4. Total Inclusion Points	A case meets the classification criteria for a diagnosis of IgG4 RD if the entry criteria are met, no exclusion criteria present, and the **total points is ≥20 (ou 19…)**

Un score d'activité: l'IgG4-RD Responder Index

IgG4-RD Responder Index Validation Study

g Rules

g refers to manifestations of disease activity present in the last 28 days

g: 0 Normal or resolved
1 Improved but still present
2 Persistent (still active; unchanged from previous visit)
3 New / Recurrence while patient is off treatment
4 Worsened or new disease manifestation despite treatment

tions

/Site score: The overall level of IgG4-RD activity within a specific organ system
omatic: Is the disease manifestation in a particular organ system symptomatic? (Y = yes; N = no)
t disease: Disease that requires treatment immediately to prevent serious organ dysfunction (Y = yes; N = no)
*ence of **urgent disease** within an organ leads to **DOUBLING** of that organ system score*)
ge: Organ dysfunction that has occurred as a result of IgG4-RD and is considered permanent (Y = yes; N = no)

	Activity			Damage	
Organ/Site	Organ/Site Score (0-4)	Symptomatic (Yes/No)	Urgent (Yes/No)	Yes/No	Symptomatic (Yes/No)

Wallace Z et al, AC&R 2018

Inspiré du BVAS dan
les vascularites à AN

=> Intérêt pour
l'évaluation de la
réponse au traiteme
lors des essais
thérapeutiques à ve

Diagnostics différentiels

Maladie associée aux IgG4: diagnostics différentiels

2

Comprehensive Clinical Diagnostic

xamen clinique : hypertrophie localisée ou diffuse au s
siquement atteints au cours de la MAG4.
iologie : élévation des IgG4 sériques (≥135 mg/dl ou 1,
istologie montrant :
nfiltration lymphocytaire et plasmocytaire polyclonale
nfiltration par des plasmocytes IgG4+ : ratio plasmo IgG
G4 définie= 1) + 2) + 3)
G4 probable= 1) + 3)
G4 possible= 1) + 2)

Un diagnostic d'excl

endant, il faudra dans tous les cas éliminer, en particul
nostics différentiels de MAG4 : tumeur maligne au sein
phome), et tableaux cliniques proches : syndrome de G
nitive, maladie de Castleman, fibrose rétro-péritonéale
oïdose, syndrome de Churg et Strauss.

ehara et al. Modern Rheumatol 2012

Table 3. Conditions that can mimic IgG4-related disease clinically and histopathologically

- Antineutrophil cytoplasmic antibody–associated vasculitides
  - Granulomatosis with polyangiitis (Wegener's)
  - Microscopic polyangiitis
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- Adenocarcinoma and squamous cell carcinoma, peritumoral infiltrate
- Castleman's disease (multicentric or localized)
- Cutaneous plasmacytosis
- Erdheim-Chester disease
- Inflammatory myofibroblastic tumor
- Inflammatory bowel disease
- Lymphoproliferative diseases
  - Extranodal marginal zone lymphomas
  - Lymphoplasmacytic lymphomas
  - Follicular lymphomas
- Perforating collagenosis
- Primary sclerosing cholangitis
- Rhinosinusitis
- Rosai-Dorfman disease
- Sarcoidosis
- Sjögren's syndrome
- Splenic sclerosing angiomatoid nodular transformation
- Xanthogranuloma

+ SHE …

Koshrohahi et al. A&

Traitement

Maladie associée aux IgG4 : Histoire naturelle et évolution sous traitement

s rémissions spontanées, mais plutôt rares…

10% *(Kamisawa et al. J Gastroenterol 2010)* à 24% *(Wakabayashi et al. Pancreas 2005)* au cours de la pancréatite A-I (P

Délai de rémission + long, % de rémission complète moins important *(Ito T et al. J Gastroenterol 2007)*

isque d'évolution vers la fibrose et la dysfonction d'organe !

Insuffisance pancréatique exocrine et/ou endocrine > 30% au cours PAI *(Maire F et al. Am J Gastroenterol*

Insuffisance rénale > 70% au cours de l'IgG4-TIN *(Raissian Y et al. J Am Soc Nephrol 2011)*

ll faut traiter !

Indications for therapy (statement 3): All patients with symptomatic, active IgG4-RD require treatment, some urgently. A subset of patients with asymptomatic IgG4-RD require treatment. (87% agreement). *Treatment of asymptomatic disease.* Subclinical disease can lead to severe, irreversible sequelae in the biliary tree, kidney, aorta, mediastinum, retroperitoneum, mesentery, and other organs (43).

However, not all manifestatio
IgG4-RD require immediate treatment. "Wa
waiting" may be appropriate, for example, in pa
with asymptomatic lymphadenopathy or mild sub
dibular gland enlargement.

rtico-sensibilité +++ (>90% de réponse, critère diagnostique pour certaines atteintes d'organes)

IgG4-RD: modalités de la corticothérapie

Remission induction with glucocorticoids (state-ent 4): Glucocorticoids are the first-line agent for remis-on induction in all patients with active, untreated G4-RD unless contraindications to such treatment are resent. (94% agreement). Prednisone at a dosage of 30– mg/day is a common initial treatment for IgG4-RD 8). The dosage may be adjusted based on body weight if the disease appears to be particularly aggressive. A

Khosroshahi et al. A&R 2015

=> 0,6 mg/kg/j

MODERN RHEUMATOLOGY, 2017
VOL. 27, NO. 5, 849–854
http://dx.doi.org/10.1080/14397595.2016.1259602

Japan College of Rheumatology
MODERN RHEUMATOLOGY
Taylc Taylor & I

ORIGINAL ARTICLE

A multicenter phase II prospective clinical trial of glucocorticoid for patients with untreated IgG4-related disease

Table 3. Outcomes of glucocorticoid treatment, in all patients, except those excluded by central review denial, and in patients diagnosed with definite IgG4-RD.

	All	%	Except denial	%	Definite only	%
ORR	55	90.2%	54	93.1%	41	93.2%
CR	38	62.3%	38	65.5%	29	65.9%
PR	17	27.9%	16	27.6%	12	27.3%
SD	2	3.3%	1	1.7%	0	0.0%
PD	1	1.6%	0	0.0%	0	0.0%
DO	3	4.9%	3	5.2%	3	6.8%
Total	61		58		44	

ORR: overall response rate; CR: complete remission; PR: partial remission; NC: no change; PD: progressive disease; DO: drop out.

Masaki et al. Mod Rheu

IgG4-RD: modalités de la corticothérapie

ephrol (2016) 20:87–93
07/s10157-015-1140-0

NAL ARTICLE

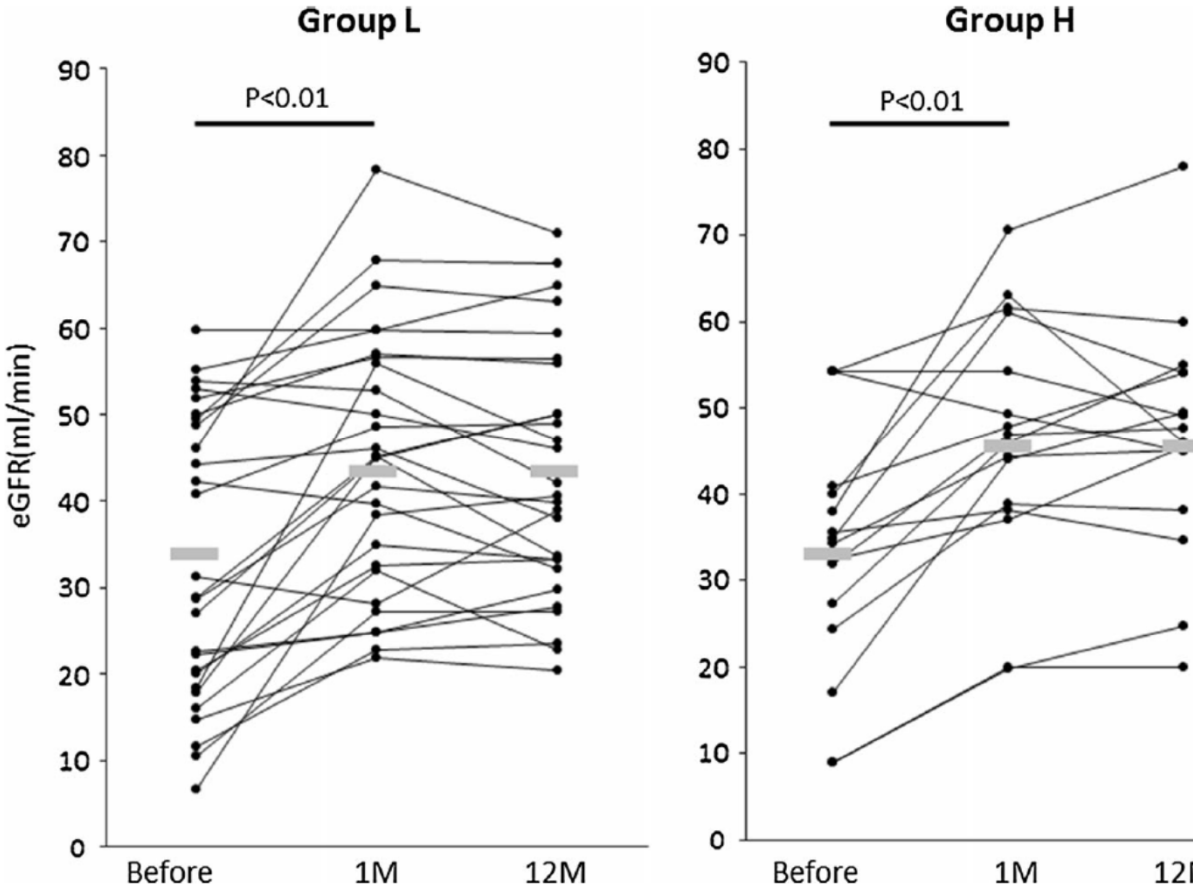
very of renal function after glucocorticoid therapy
G4-related kidney disease with renal dysfunction

Saeki[1] · Mitsuhiro Kawano[2] · Ichiro Mizushima[2] · Motohisa Yamamoto[3] ·
da[4] · Yoshifumi Ubara[5] · Hitoshi Nakashima[6] · Tomoyuki Ito[1] ·
Yamazaki[1] · Ichiei Narita[4] · Takao Saito[7]

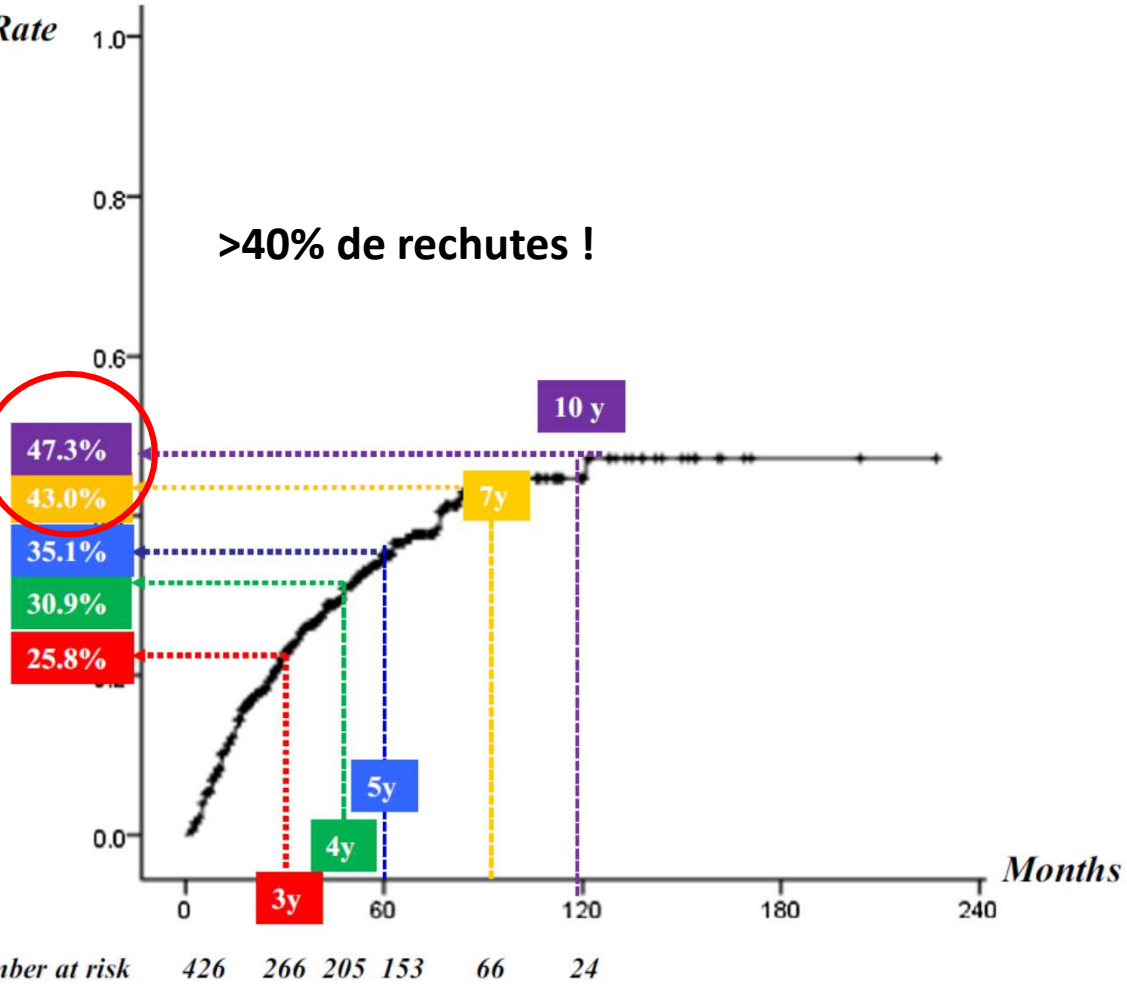
=> Pas de bénéfice à une posologie initiale de CTC > 0,6 mg/kg/j

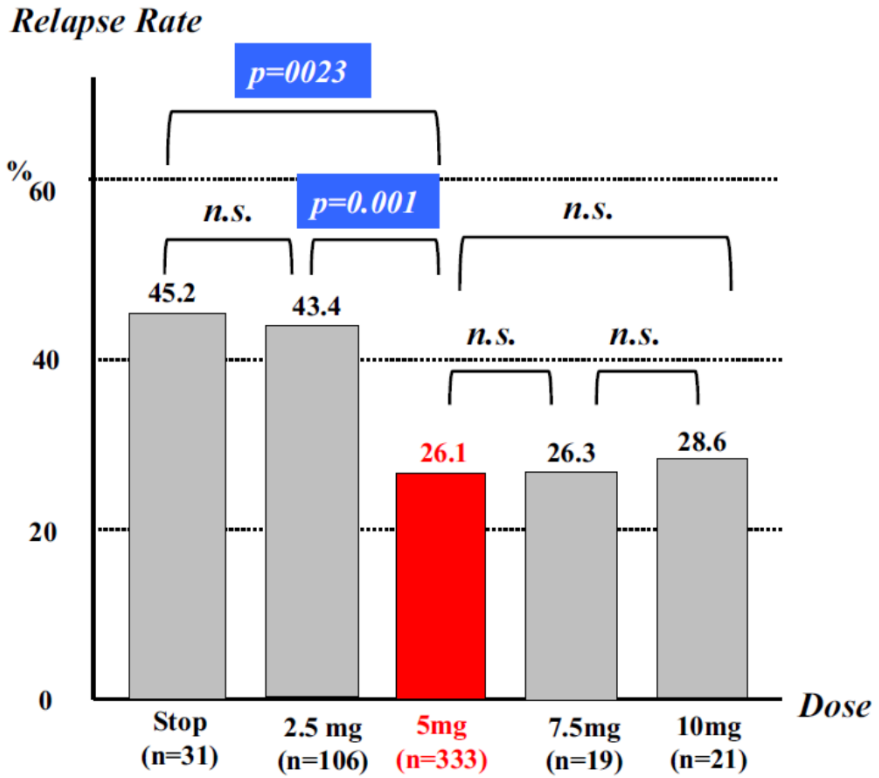
≤ 0,6 mg/kg/j (n=27)

> 0,6 mg/kg/j (n=16)



IgG4-RD: rechutes et cortico-dépendance…





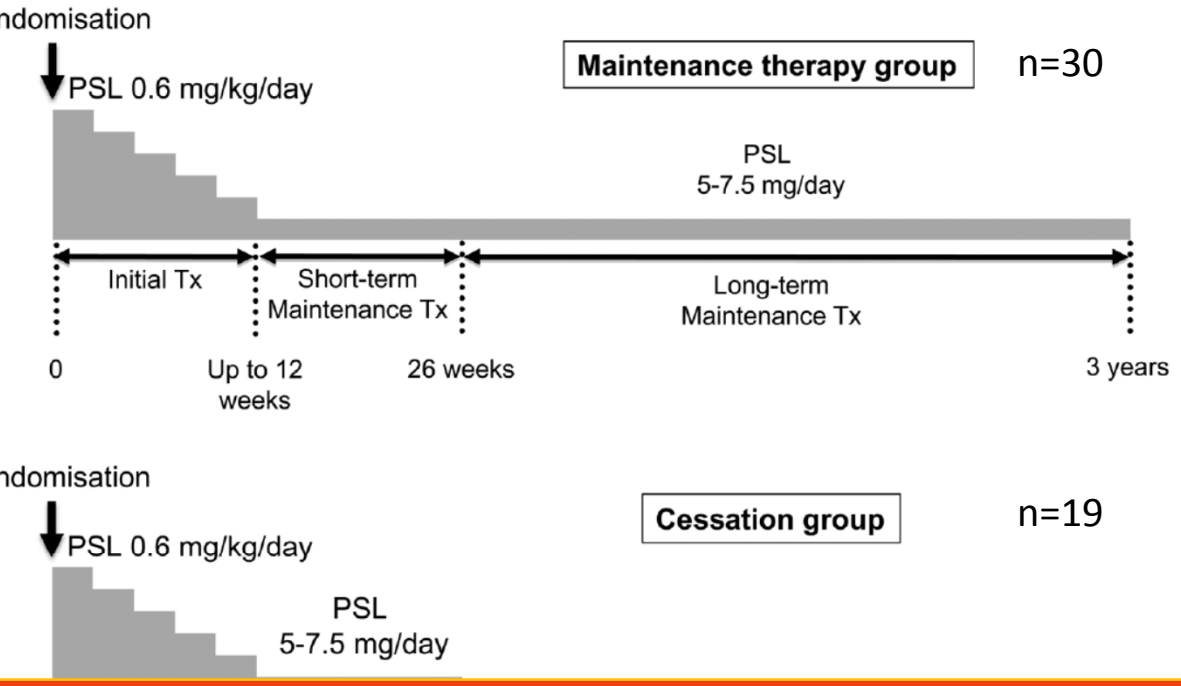
Cortico-dépendance ++
Corticothérapie d'entretien

Kubota K et al. J Gastroenterol 2017

GINAL ARTICLE

ndomised controlled trial of long-term aintenance corticosteroid therapy in patients th autoimmune pancreatitis

Masamune et al, Gut 2016



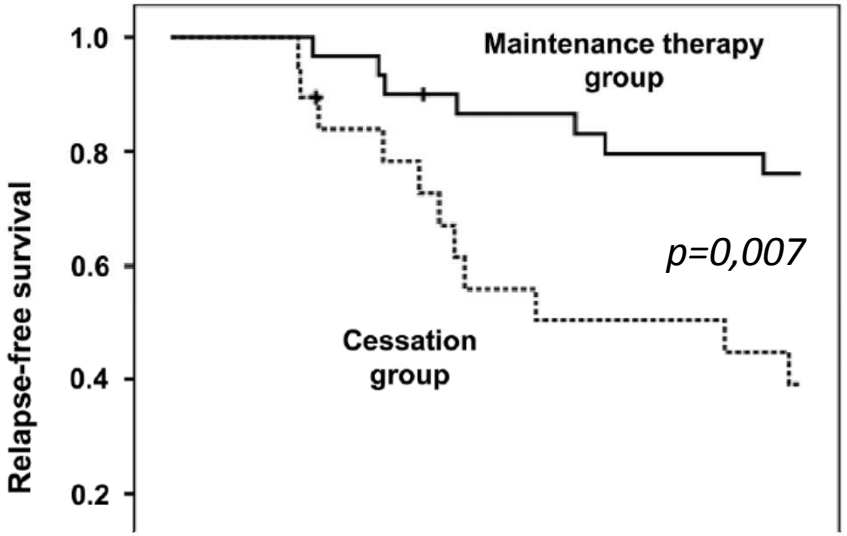


Table 4. Adverse events observed during glucocorticoid treatment in pati with IgG4-RD.

Adverse events	Number of cases	%
Expected		
Glucose intolerance	25	41
Newly diagnosed with DM	12	19
Aggravation from chronic DM	13	21
Infection	11	18
Fungus	6	9.
Bacteria	3	4.
Virus	1	1.
Acid-fast Bacillus	1	1.
Dyslipidemia	16	26
Hypertension	9	14

- Nécessité de développer de nouvelles stratégies thérapeutiques d'épargne cortisoniqu +++

Masaki et al, Mod Rheuma

IgG4-RD:
Place des immunosuppresseurs « usuels » / DMARDs ?

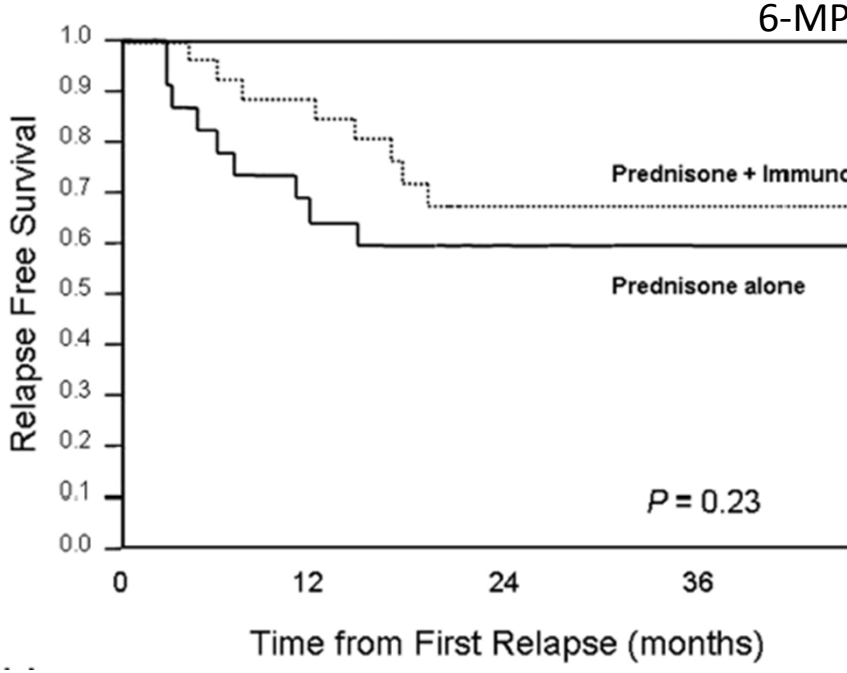
ABLE 6. Treatment and Efficacy

reatment	Patients Treated No. (%)	Treatment Effective No. (%)	Side Effects No. (%)
orticosteroids	23 (92)	19/21* (90)	14/21* (67)
zathioprine	6 (24)	3/4* (75)	1/4* (25)
ituximab	3 (12)	2/3 (67)	0/3 (0)
yclophosphamide	3 (12)	1/3 (33)	1/3 (33)
lethotrexate	2 (8)	1/2 (50)	0/2 (0)
ther			
Surgery	4 (16)	1/4 (25)	1/4 (25)
epatic transplantation	1 (4)	0/1 (0)	1/1 (100)
Vinblastine	2 (8)	0/2 (0)	0/2 (0)
Tamoxifen	1 (4)	0/1 (0)	1/1 (100)
Tocilizumab	1 (4)	1/1 (100)	0/1 (0)
Imatinib	1 (4)	0/1 (0)	0/1 (0)

*Recent treatment for 2 patients, response and tolerance not yet evaluable.

Ebbo et al. Medicine 2012

Azathiop
MMF
6-MP



Hart et al. Gut 20

IgG4-RD et rituximab

RD

Rituximab for IgG4-related disease: a prospective, open-label trial

Mollie N Carruthers, Mark D Topazian, Arezou Khosroshahi, Thomas E Witzig, Zachary S Wallace, Philip A Hart, Vikram Deshpande, Thomas C Smyrk, Suresh Chari and John H Stone

Ann Rheum Dis 2015 74: 1171-1177 originally published online February

=30

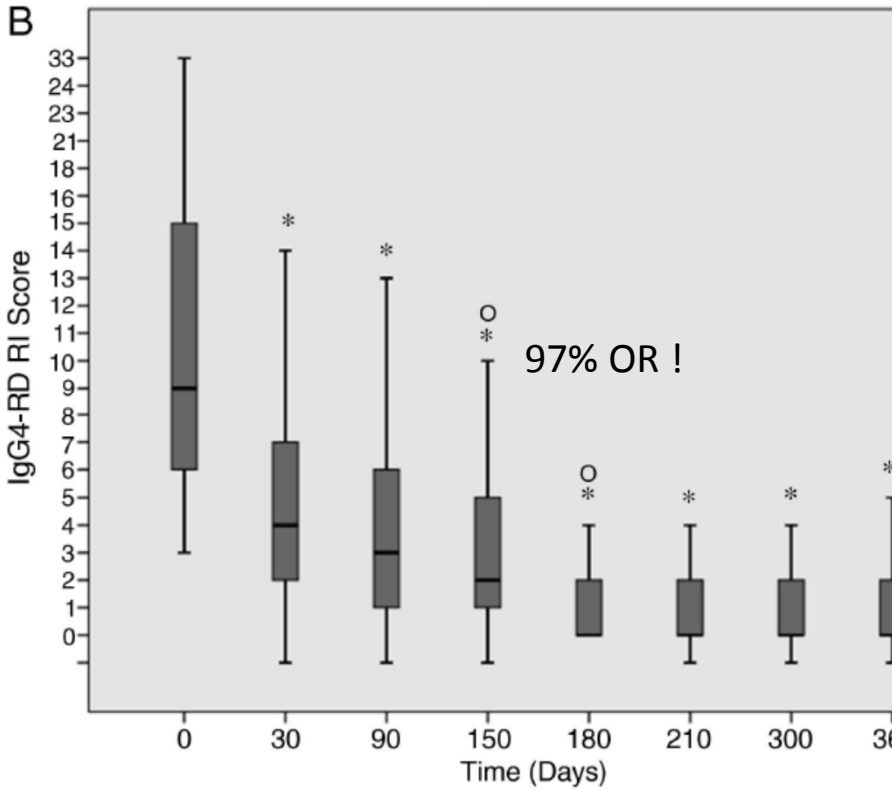
7% RTX seul

bjectif I[aire] à M6: IgG4RD-RI ↘ ≥2 ; pas de rechute ; pas de CTC entre

› 77% des patients à M6, bonne tolérance

lais…

› 7 rechutes, pas de suivi après M12…



IgG4-RD et rituximab

nnées dans la « vrai vie », avec plus de suivi ?

Cohorte française: n=33 patients traités par RTX

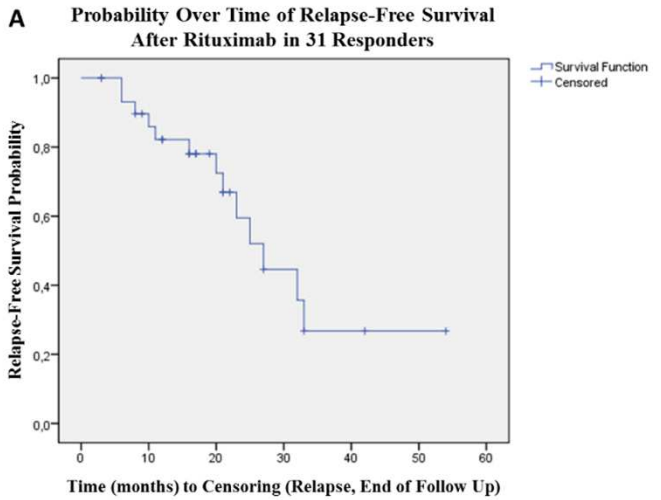
Réponse chez 93,5% des patients

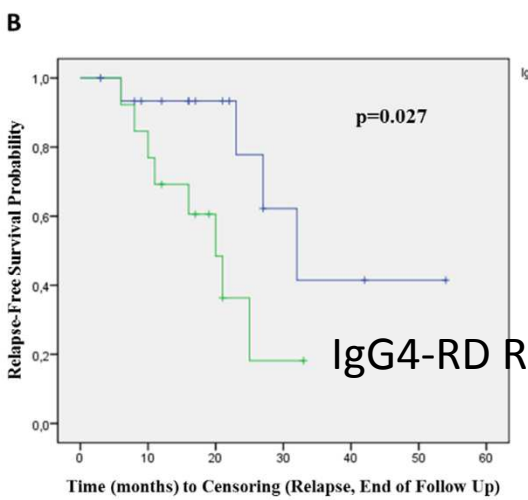
is…

Suivi de 24,8 mois: 41,9% de rechute
(délai médian de 19 mois)

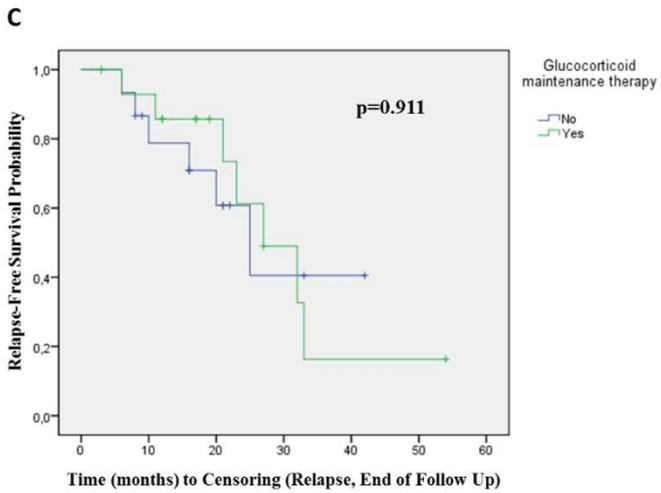
ux d'infections sévères: 12,1/100 patient-années
3 patients hypogamma ≤ 5 g/L

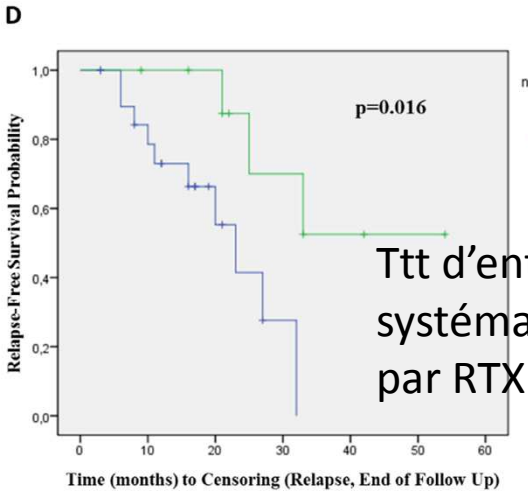
Ebbo et al, PLoS ONE 2017





IgG4-RD R





Ttt d'en
systéma
par RTX

Take Home Messages

es localisations pseudo-tumorales, uniques ou multiples

Absence de marqueur biologique spécifique, mais des lésions histologiques communes

Des présentations cliniques multiples, de nombreux diagnostics différentiels

Des critères de classification « validés » (ACR/EULAR) à venir

Corticosensibilité ++ mais rechutes… traitements de 2nde ligne non consensuels

Avancées physiopathologiques, traitements ciblés?

Cohorte française de l'IgG4-RD: > 250 patients

e-CRF national

mikael.ebbo@ap-hm.fr