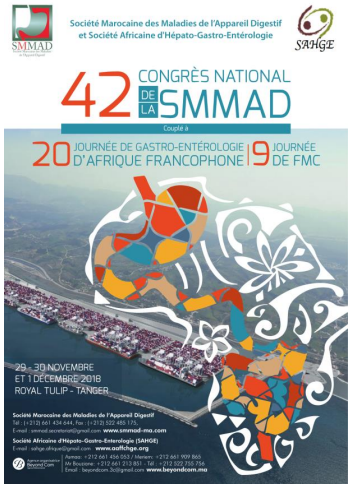

Cholangite à IgG4

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Service d'hépatogastroentérologie
CHU Mohammed VI
OUJDA

Objectifs pédagogiques

Quand penser à la cholangite à IgG4?
Comment faire le diagnostic différentiel avec CSP et CCA?
Quels sont les critères diagnostiques de la cholangite à IgG4?
Quel traitement proposer?
Quel pronostic?

Cholangite à IgG4 (IgG4 related sclerosing cholangitis; IgG4-SC)

Entité récente

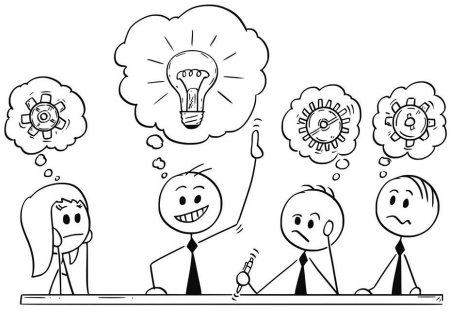
Maladie sclérosante à IgG4 (IgG4-Related disease; IgG4-RD) : atteinte multiorgane

Maladie bénigne mais fibrose → insuffisance d'organes

P. Brito-Zerón et al. / Autoimmunity Reviews 13 (2014) 1203–1210

Approche multidisciplinaire +++

Clé = y penser !!

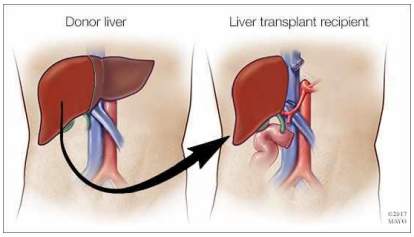


Difficulté diagnostique = similitude avec CSP et CCA

IgG4 sérique +++

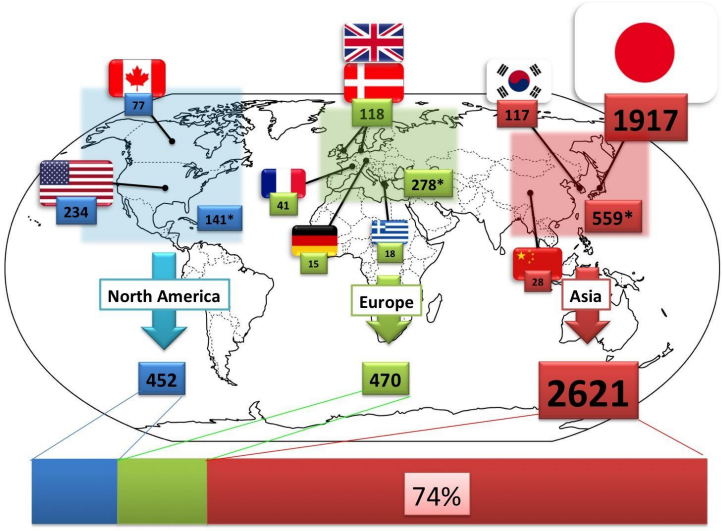
Traitement et pronostic # CSP et CCA

Corticosensible # CSP



Maladie à IgG4

ASIE ++++
EUROPE / AMERIQUE



IgG4-SC Epidémiologie

Region	Year	N	Male (%)	Age at presentation (years)
USA [1]	2008	53	85	62[a]
UK [2]	2014	68	74	61[b]
Japan [3]	2017	527	83	66[b]

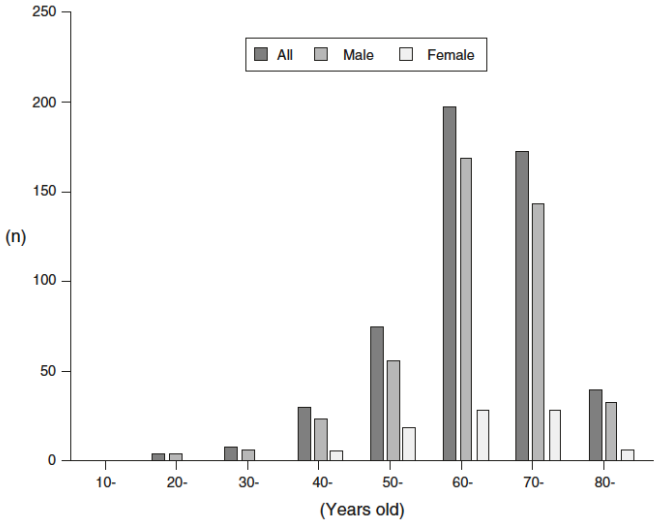
[a]Average
[b]Median

IgG4-related scelrosing cholangitis.T.Kamisawa, M.Kim. Springer. 2019

Sex ratio 4.8: 1

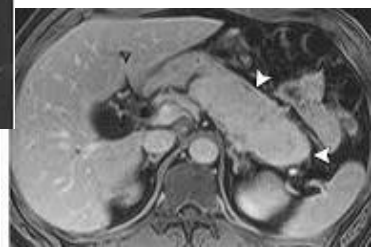
Age médian 66 ans

« blue collar » disease (industrie, solvants , huiles ...)

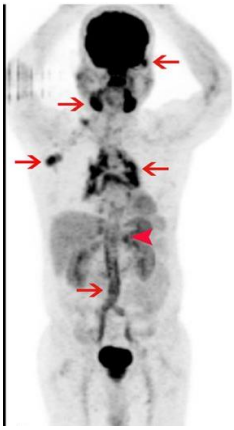


IgG4-related scelrosing cholangitis.T.Kamisawa, M.Kim. Springer. 2019

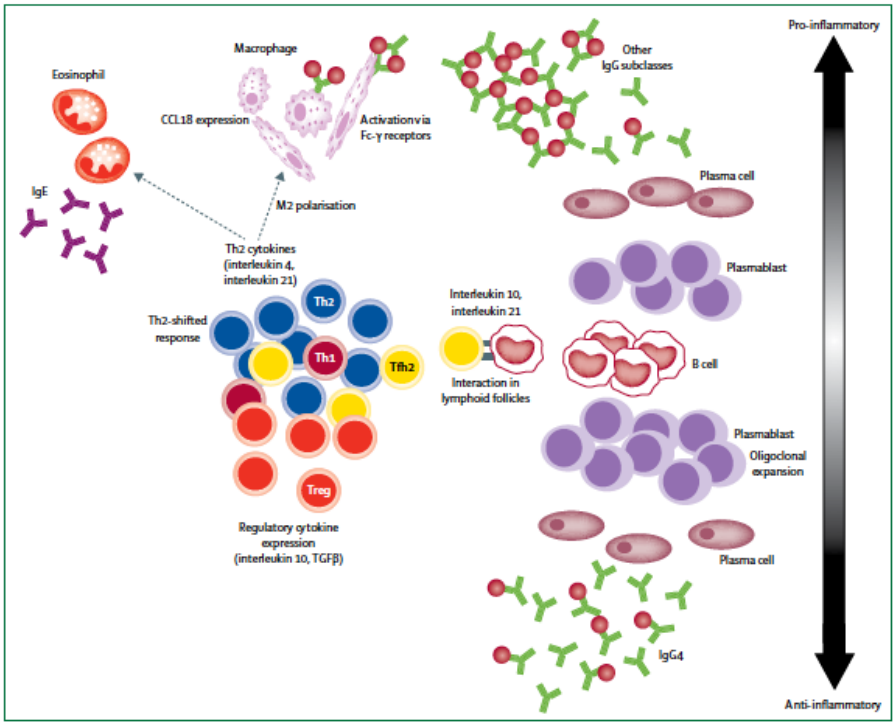
87% associée à pancréatite autoimmune



90% autre atteinte IgG4 RD



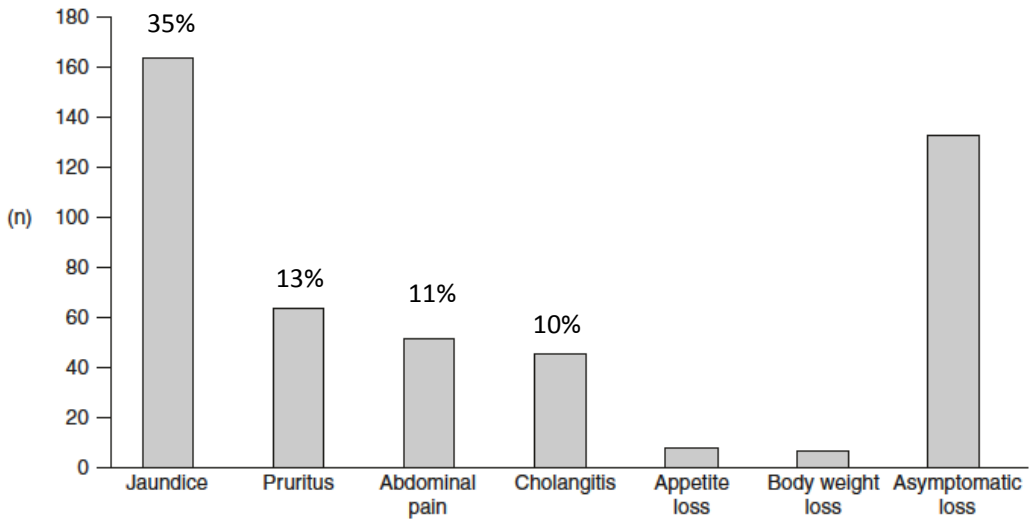
64% limitée à la portion intrapancréatique de la VBP



Lancet Gastroenterol Hepatol
2018; 3: 575–85

Aucun symptôme spécifique

Ictère fluctuant ++++



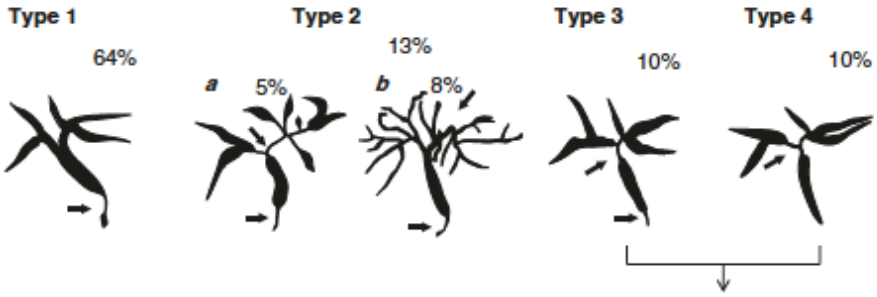
Tanaka.Clin Gastroenterol Hepatol (2017), 15(6):920-926

Diagnostic = éliminer les principaux diagnostics différentiels

Cholangite sclérosante primitive (PSC)
Cholangiocarcinome (CCA)

Démarche en fonction du type de IgG4-SC

	IgG4-SC	**PSC**	**CCA**
Sexe	Homme	Homme	Homme
Age	6° décade	3°-4° décade	7° décade
symptômes	Ictère +++ Fluctuant parfois AEG Asymptomatique 28%	Anomalies BH 47% Ictère 13% Doul abdo 29% Prurit 7%	Ictère Doul abdo AEG
Autres organes	Pancréas ++ Atteinte IgG4-RD MICI <10%	MICI 60-80% (Ouest)	Métastases



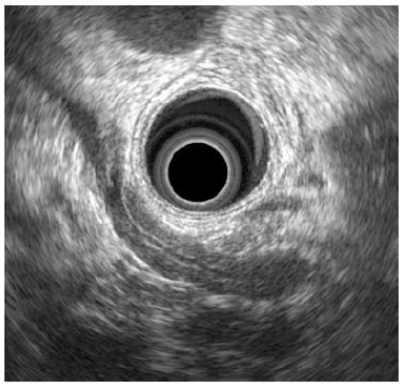
	Type 1	Type 2	Type 3	Type 4
Differential diagnosis	Pancreatic cancer Bile duct cancer Chronic pancreatitis	Primary sclerosing cholangitis	Bile duct cancer Gallbladder cancer	
Useful modalities	IDUS* (bile duct) EUS-FNA** (pancreas) Biopsy (bile duct)	Liver biopsy Colonoscopy (R/O coexistence of IBD ***)	EUS (bile duct, pancreas) IDUS (bile duct) Biopsy (bile duct)	

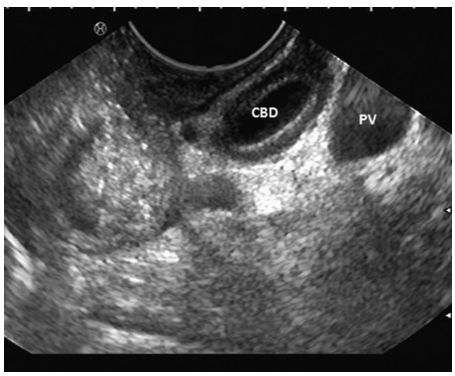
Type 1

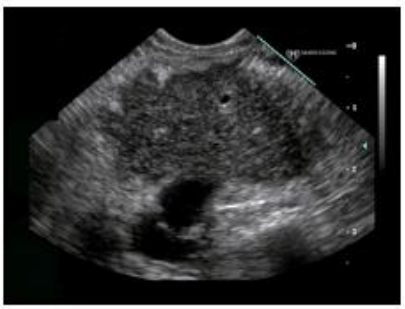
64%

Pancreatic cancer
Bile duct cancer
Chronic pancreatitis

IDUS* (bile duct)
EUS-FNA** (pancreas)
Biopsy (bile duct)







PAI associée

FNA → Eliminer cancer
Infiltrat lymphoplasmocytaire

FNB → critères diagnostiques :

-Cellules IgG4+ >10 / HPF
-Ratio IgG4+/IgG+ > 40%

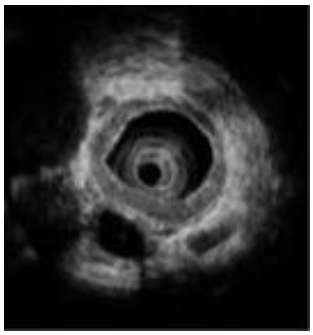
Type 1

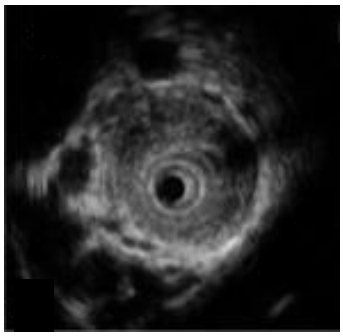
64%

Pancreatic cancer
Bile duct cancer
Chronic pancreatitis

IDUS* (bile duct)
EUS-FNA** (pancreas)
Biopsy (bile duct)

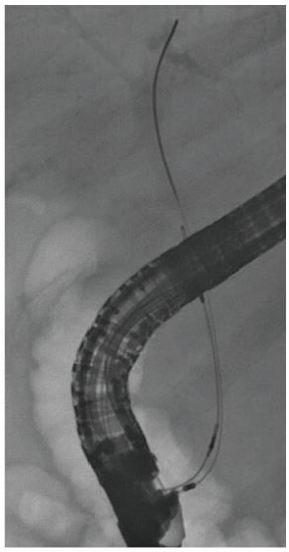
Eus endocanalaire (IDUS)



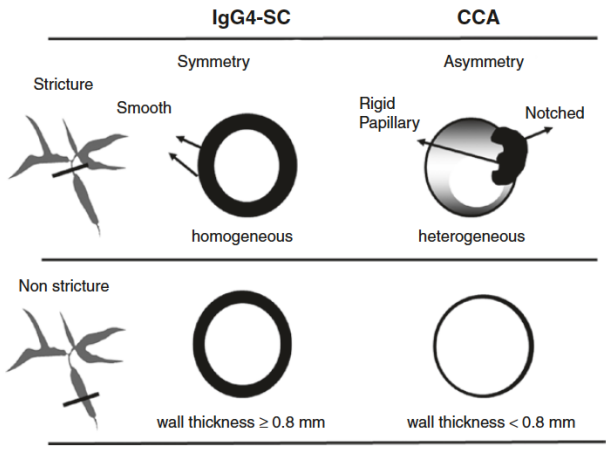


CPRE : brossage/biopsie

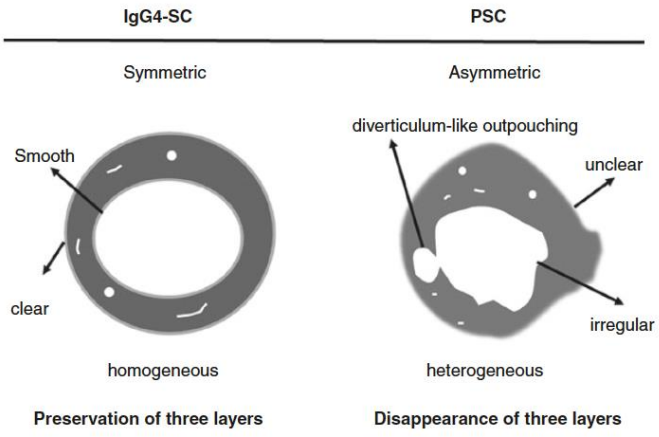
Forceps biopsy

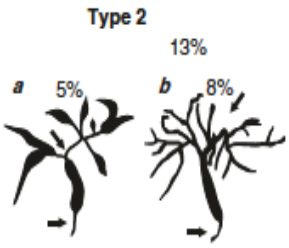


Brush



Echoendoscopie endocanalaire
IDUS

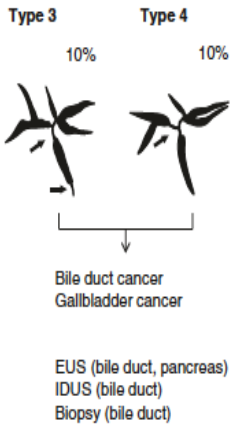




Primary sclerosing cholangitis

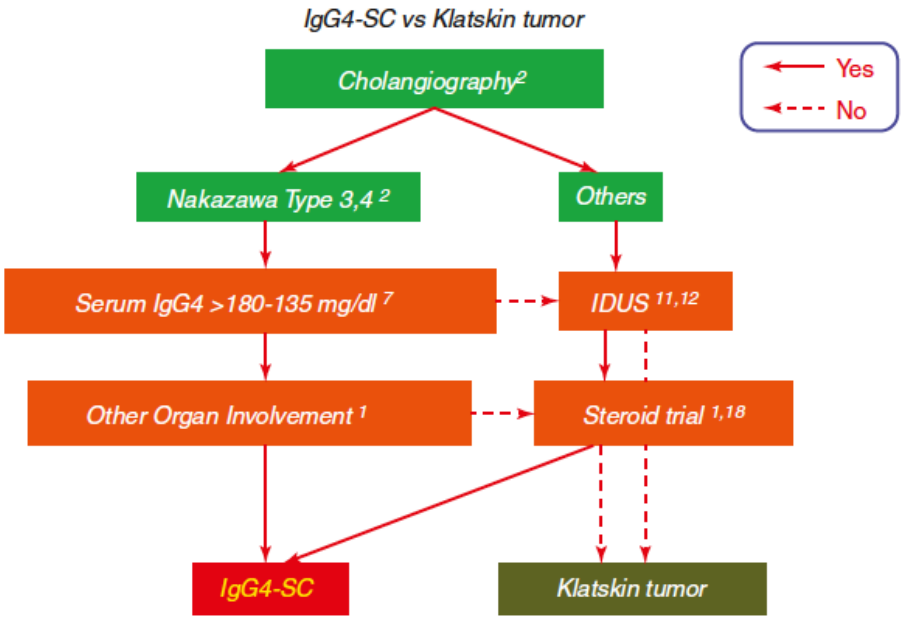
Liver biopsy
Colonoscopy
(R/O coexistence of IBD ***)

	Favor PSC	Favor IgG4-SC
Age	<40 years[a]	>60 years
Inflammatory bowel disease	Presence[a]	–
Serum IgG4	<140 mg/dL	>560 mg/dL[a]
Serum IgG4:IgG1 ratio[b]	<0.24	>0.24
pANCA	Positive	–
Association with autoimmune pancreatitis/IgG4-related disease	–	Presence[a]
Cholangiogram	Beaded appearance, diverticulum-like outpouching, pruned tree appearance	Longer stricture and more prestenotic dilatation, distal CBD stricture
Cholangioscopy	Scarring and pseudodiverticula	Dilated and tortuous vessel
Intraductal ultrasonography	Irregular inner margin, disappearance of three layers	Symmetrically thickened wall with smooth margin
Histology and immunohistochemistry	Onion-skin fibrosis and periportal sclerosis, sometimes IgG4-positive cell infiltration	Dense and richly IgG4-postive lymphoplasmacytic infiltration, marked fibrosis with storiform pattern, and obliterative phlebitis
Tissue IgG4+:IgG+ plasma cell ratio	<0.40	>0.40 {with IgG4+ plasma cells >10/HPF (biopsy) or 50/HPF (resection)}
Steroid responsiveness[c]	–	Positive[a]



Procedures	IgG4-related sclerosing cholangitis (IgG4-SC)	Klatskin tumor
Serum IgG4	>180–135 mg/dl [7]	<135 mg/dl [8]
Serum CA19-9	Almost within normal limits	Elevated [3]
US	Three-layer or parenchymal-echo type bile duct wall thickness [10]	Mass lesion in the bile duct [3]
EUS	Bile duct wall thickening in narrowed duct segments	Mass lesion in the bile duct [3]
IDUS	Continuous symmetric wall thickening with smooth outer and inner margins associated with homogeneous internal echo which spreads to hilar lesion [11, 12]	Mass lesion in the bile duct [3] (lateral-spreading type cancer mimic IgG4-SC)
CT	Single-layered enhancement (not obstructed completely) [13]	Dual-layered enhancement [13]
PET-CT	Positive and it decreased after steroid treatment	Positive
Cholangiography	Long stricture of the bile duct [2]	Segmental obstruction of the bile duct [3]
POCS	Dilated or tortuous vessels [16]	Partially dilated vessels with enhancement and fusion [16]
Endoscopic biopsy	Difficult to get sufficient material [12]	40–80% positivity for cancer [3, 17]
Steroid trial	Positive [1, 18]	Negative
Resected specimens	1. Lymphoplasmacytes infiltration and fibrosis [1, 7, 9]	Cancer cell
	2. IgG4-positive lymphoplasma cell infiltration [1, 7, 9]	
	3. Obliterative phlebitis [1, 7, 9]	
	4. Storiform fibrosis [1, 7, 9]	

IgG4-SC IgG4-related sclerosing cholangitis, *US* ultrasonography, *EUS* endoscopic ultrasonography, *IDUS* intraductal ultrasonography, *CT* computed tomography, *PET-CT* position-emission tomography in combination with computed tomography, *POSC* peroral video cholangioscopy


IgG4-SC vs Klatskin tumor
Cholangiography[2]
Yes
No
Nakazawa Type 3,4 [2]
Others
Serum IgG4 >180-135 mg/dl [7]
IDUS [11,12]
Other Organ Involvement [1]
Steroid trial [1,18]
IgG4-SC
Klatskin tumor

Diagnostic non invasif possible?

Scoring system to differentiate between PSC and IAC

Criteria	0 Points	1 Point	2 Points	3 Points	4 Points
Age, years	<30	30–39	40–49	50–59	≥60
Multi-organ affection	No	–	–	Yes	–
"Pearl necklace" in the MRCP-based cholangiogram	Yes	–	No	–	–

0–4 points: PSC probable.
5–6 points: steroid therapy trial.
7–9 points: IAC probable.

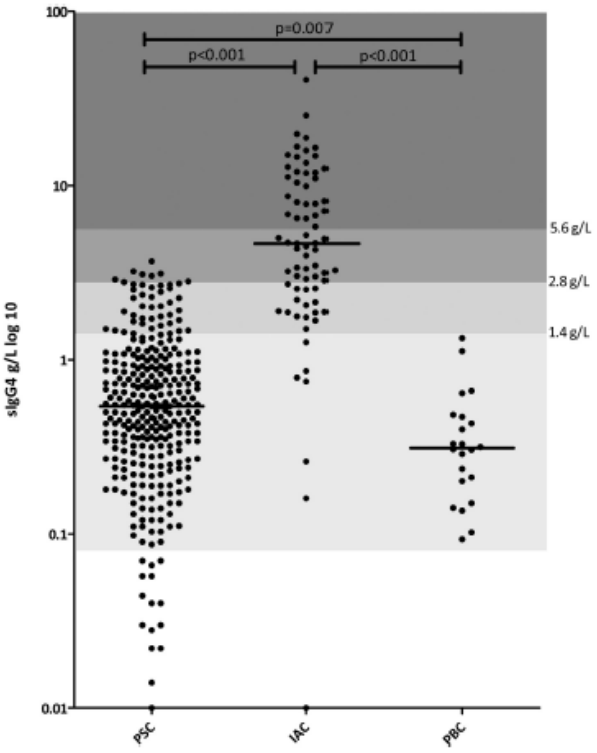
Rôle des IgG4 sériques

Performance of serum IgG4 in distinguishing IgG4-SC from CC and PSC

	IgG4 cutoff value (mg/dl)	Sensitivity (%)	Specificity (%)	Citation
IgG4-SC vs. CC	138	89.8	92.6	14
	140	78	87	16
	280	50	97	
	560	26	100	
IgG4-SC vs. PSC	117	91.5	87.6	14
	140	90	85	15
	250	89	95	
	250	67[a]	95[a]	
	280	70	98	
	560	42	100	

[a]Validation cohort

IgG4-related scelrosing cholangitis.T.Kamisawa, M.Kim. Springer. 2019



IgG4 sérique > 1,4g/l dans 15% des PSC

HEPATOLOGY 2014;59:1954-1963

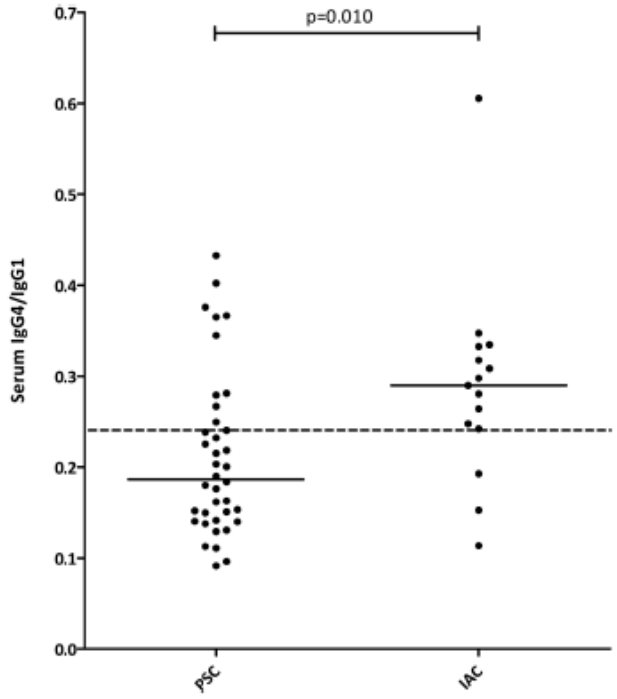
Rapport IgG4/IgG1

Si IgG4 1,4-2,8g/l

cut off 0,24

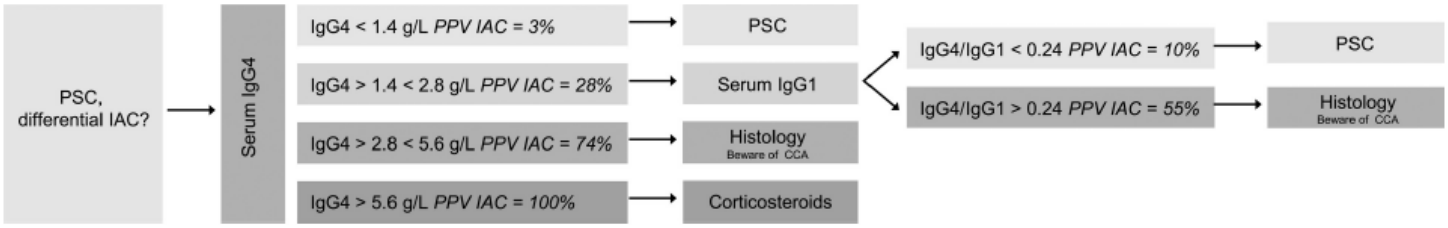
se 86%

sp 95%



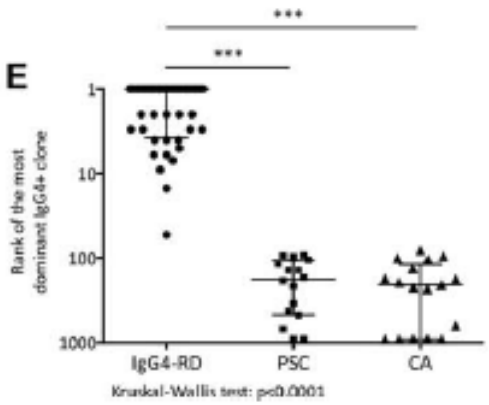
HEPATOLOGY 2014;59:1954-1963

Proposition Algorithme en fonction IgG4 et ratio IgG4/IgG1

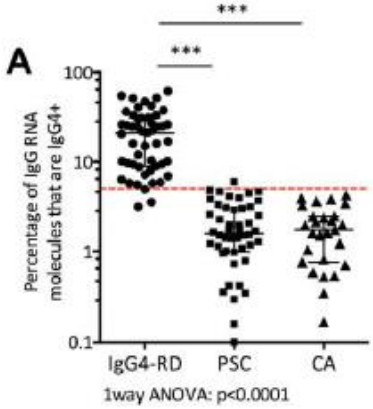


HEPATOLOGY 2014;59:1954-1963

Nouvelles techniques



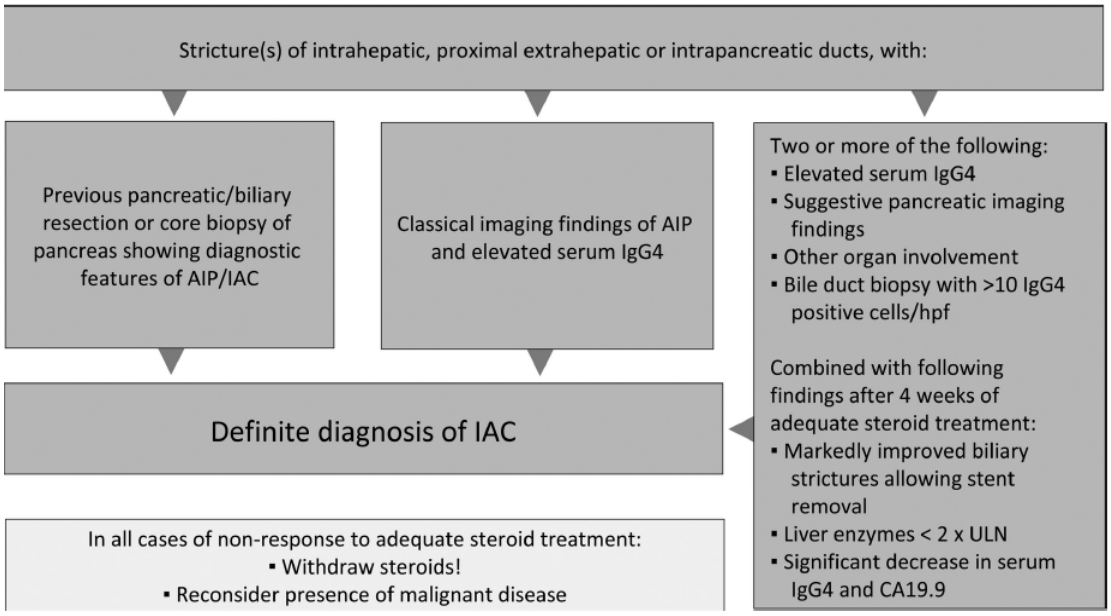
IgG4+ BCR clones



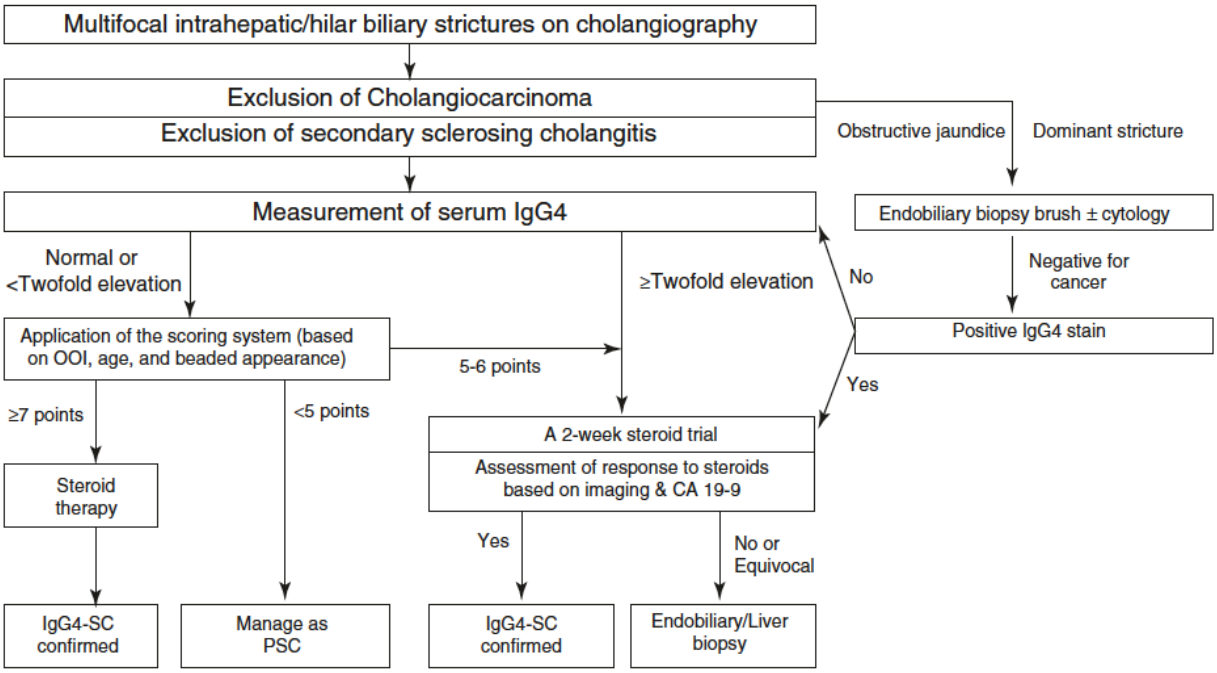
qPCR IgG4 RNA molecules

HEPATOLOGY 2016;64:501-507

Critères diagnostiques HISORt adaptés à l'IgG4-SC



HEPATOLOGY 2014;59:1954-1963



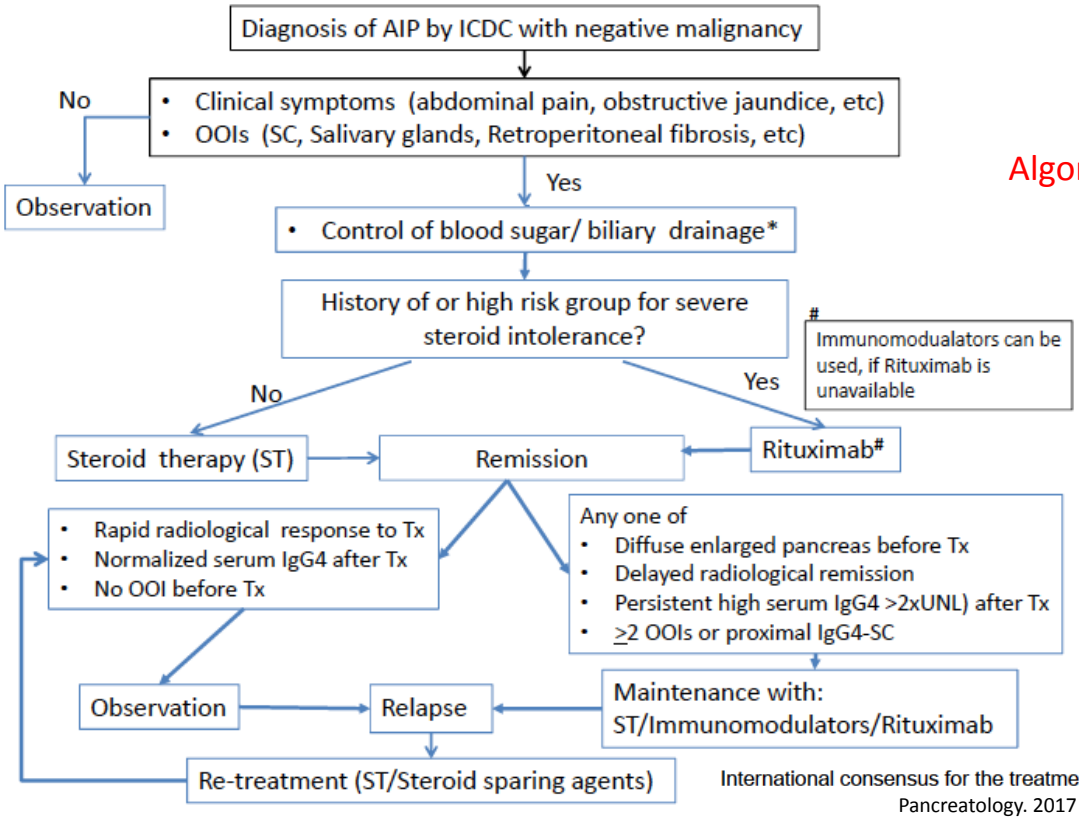
IgG4-related scelrosing cholangitis.T.Kamisawa, M.Kim. Springer. 2019

IgG4-related disease manifestations in which urgent treatment is recommended

Manifestation	Rationale for urgent treatment
Aortitis	Inflammatory aortic aneurysms can continue to enlarge and are at risk for dissection.
Retroperitoneal fibrosis	Progressive disease may lead to irreversible nerve damage/pain and/or ureteral obstruction/renal failure.
Proximal biliary strictures*	Untreated disease may lead to superimposed infectious cholangitis and eventually irreversible fibrosis and cirrhosis.
Tubulointerstitial nephritis	Untreated disease may lead to irreversible chronic kidney disease.
Pachymeningitis	Untreated disease puts the patient at risk for neurologic deficits and/or seizures.
Pancreatic enlargement	Untreated disease may lead to irreversible pancreatic exocrine and endocrine failure.
Pericarditis	Untreated disease may lead to tamponade or constrictive pericarditis

* "Proximal" denotes involvement of the intrahepatic bile ducts or extrahepatic portion of the common bile duct that is superior to the intrapancreatic portion.

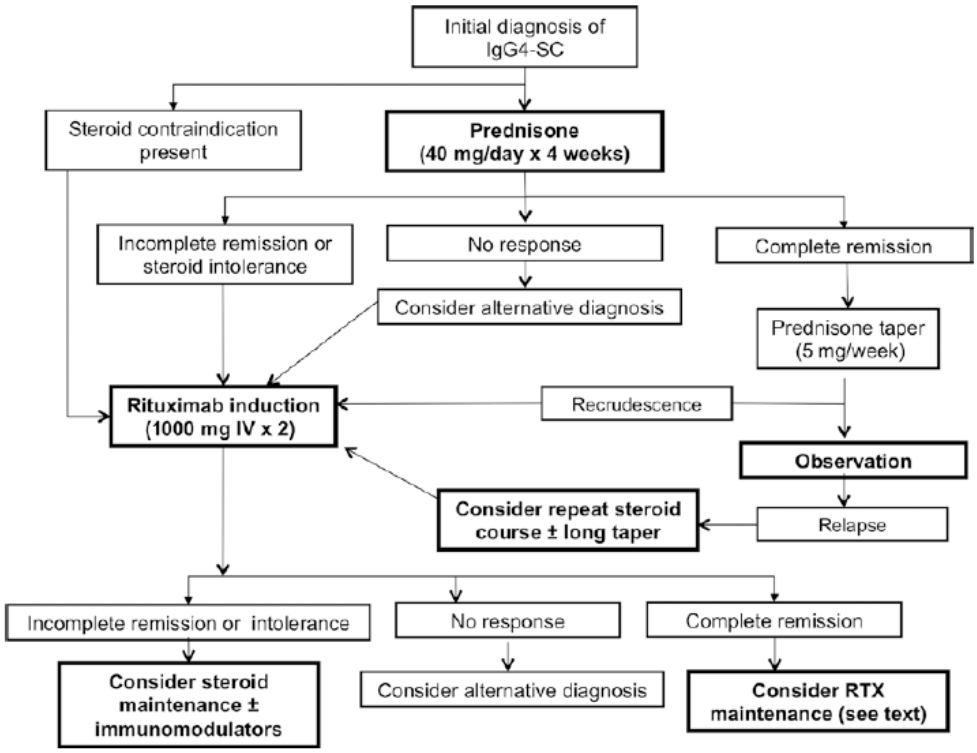
ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 7, July 2015, pp 1688–1699



Algorithme IgG4- AIP

International consensus for the treatment of autoimmune pancreatitis
Pancreatology. 2017 Jan - Feb;17(1):1-6.

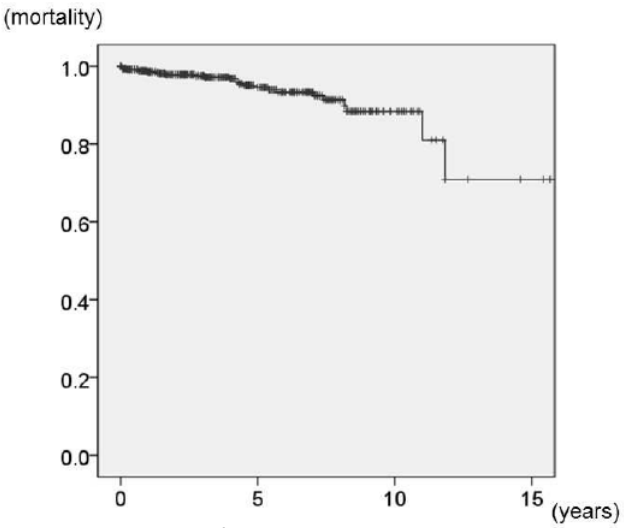
Algorithme IgG4-SC



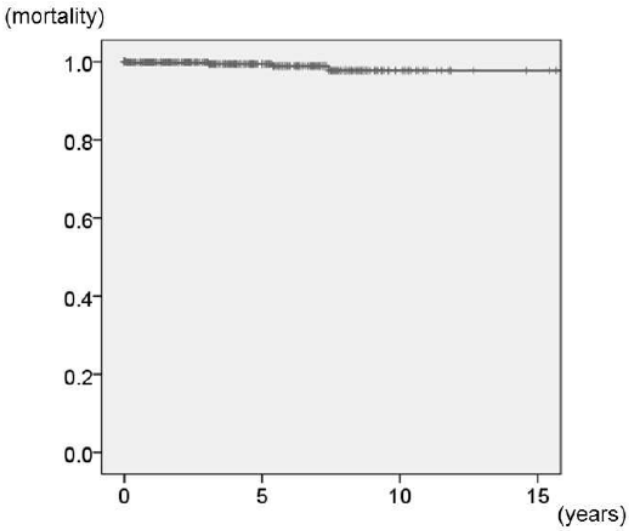
T.Kamisawa, M.Kim. IgG4-related scelrosing cholangitis. Springer. 2019

Cohorte japonaise IgG4-SC

Taux de rechute 19%



Mortalité IgG4-SC de toutes causes



Mortalité IgG4-SC hépatobiliaire

Tanaka.Clin Gastroenterol Hepatol (2017), 15(6):920-926

CAS CLINIQUES