Hépatopathies à IgG4: Points Clés

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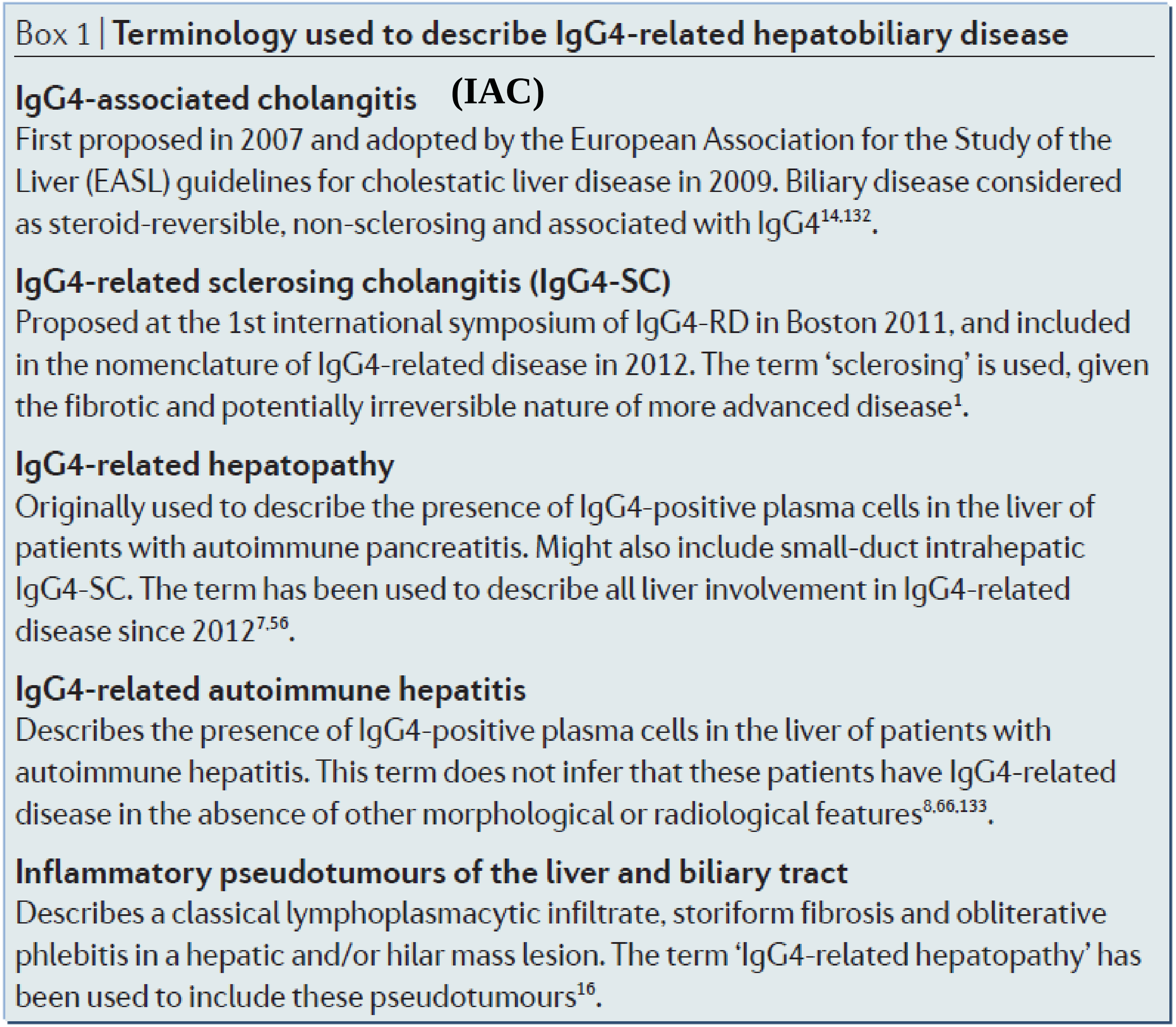
Maladie IgG4 et Foie: Terminologie



Box 1 | **Terminology used to describe IgG4-related hepatobiliary disease**

IgG4-associated cholangitis **(IAC)**

First proposed in 2007 and adopted by the European Association for the Study of the Liver (EASL) guidelines for cholestatic liver disease in 2009. Biliary disease considered as steroid-reversible, non-sclerosing and associated with IgG4[14,132].

IgG4-related sclerosing cholangitis (IgG4-SC)

Proposed at the 1st international symposium of IgG4-RD in Boston 2011, and included in the nomenclature of IgG4-related disease in 2012. The term 'sclerosing' is used, given the fibrotic and potentially irreversible nature of more advanced disease[1].

IgG4-related hepatopathy

Originally used to describe the presence of IgG4-positive plasma cells in the liver of patients with autoimmune pancreatitis. Might also include small-duct intrahepatic IgG4-SC. The term has been used to describe all liver involvement in IgG4-related disease since 2012[7,56].

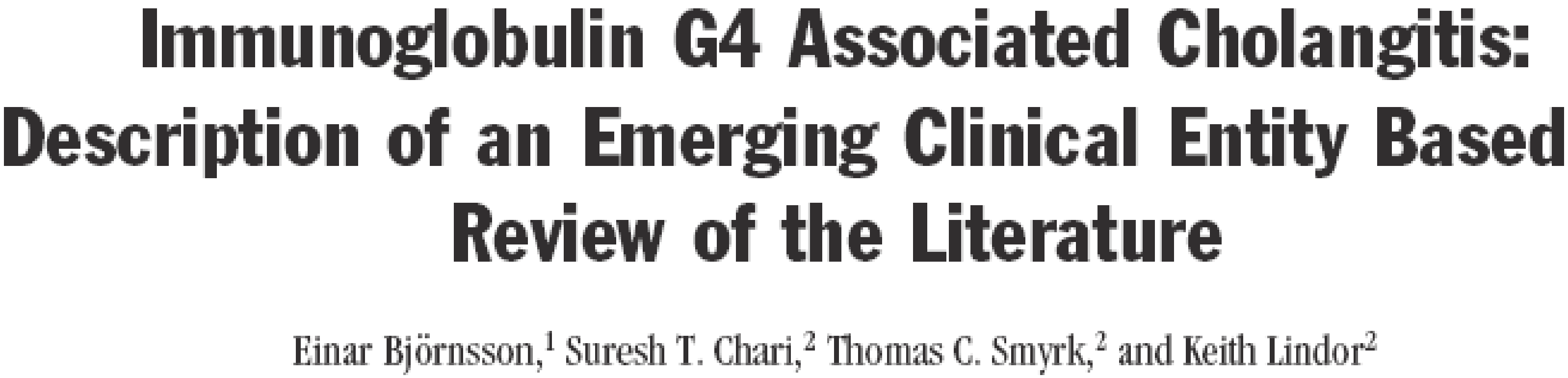
IgG4-related autoimmune hepatitis

Describes the presence of IgG4-positive plasma cells in the liver of patients with autoimmune hepatitis. This term does not infer that these patients have IgG4-related disease in the absence of other morphological or radiological features[8,66,133].

Inflammatory pseudotumours of the liver and biliary tract

Describes a classical lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis in a hepatic and/or hilar mass lesion. The term 'IgG4-related hepatopathy' has been used to include these pseudotumours[16].

(Culver et al, Nat Rev Gastroenterol Hepatol 2016)



Immunoglobulin G4 Associated Cholangitis: Description of an Emerging Clinical Entity Based on Review of the Literature

IAC

Einar Björnsson,[1] Suresh T. Chari,[2] Thomas C. Smyrk,[2] and Keith Lindor[2]

(Hepatology 2007)

Pancréato-cholangite sclérosante ou autoimmune,

Cholangite sclérosante associée à une pancréatite autoimmune,

Cholangite sclérosante autoimmune …

IgG4-related (sclerosing) cholangitis (IgG4-SC)

IgG4 cholangiopathy

Atteinte biliaire de
l’IgG4-related (systemic) disease (IgG4-RD)

IgG4-RD (1)

Affection fibro-inflammatoire caractérisée par:

- **Tuméfaction(s)**
- **Infiltrat lympho-plasmocytaire riche en plasmocytes IgG4+**
- **« storiform fibrosis »**
- **Augmentation fréquente mais inconstante des IgG4 sériques**

➡ **Maladie fibro-inflammatoire pouvant intéresser pratiquement tous les organes (≈ sarcoïdose): pancréas, glandes salivaires, reins, poumons, aorte, ganglions, prostate…**

(Stone et al, N Engl J Med 2012)

IgG4-RD (2)

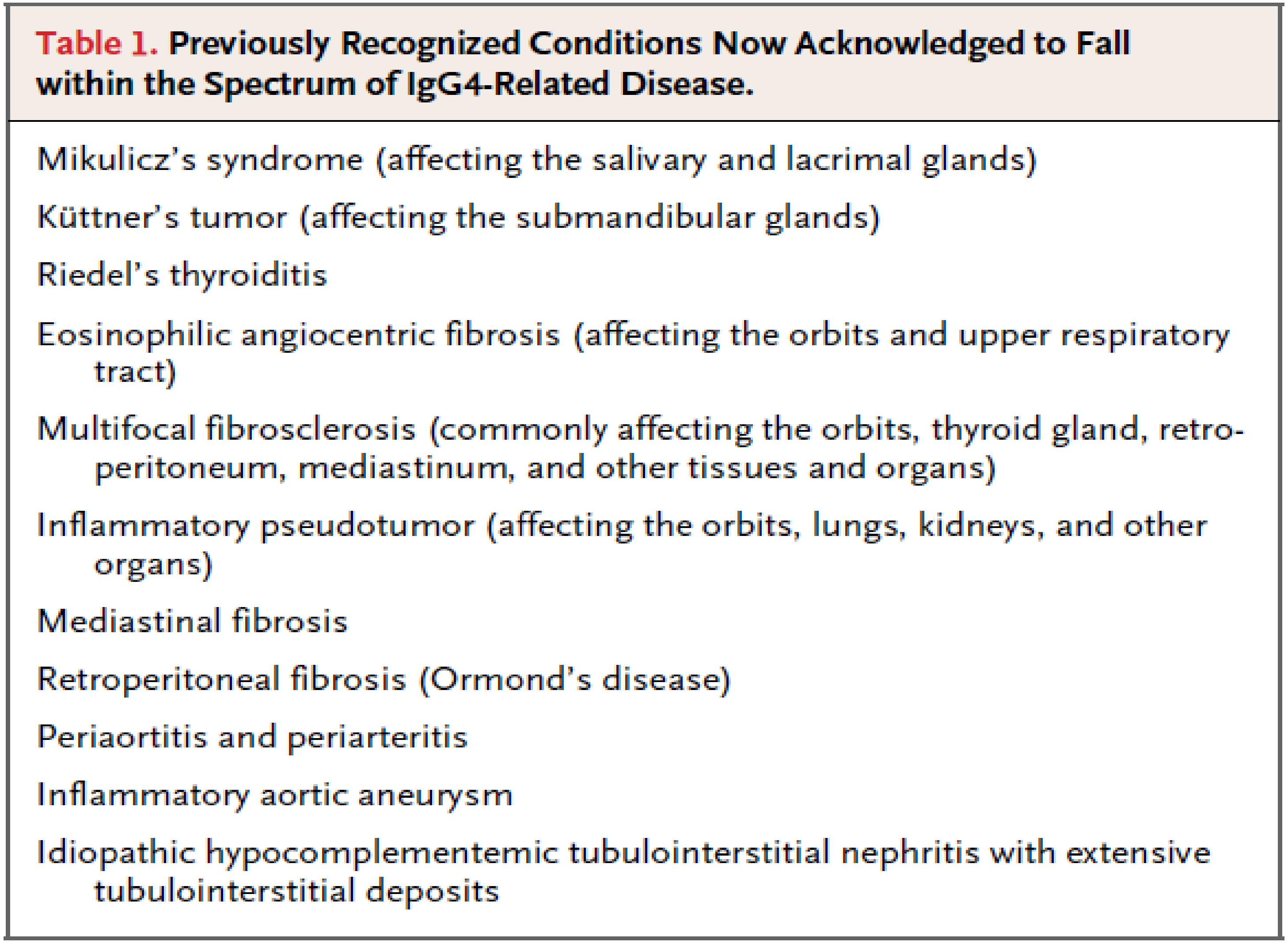


Table 1. Previously Recognized Conditions Now Acknowledged to Fall within the Spectrum of IgG4-Related Disease.

Mikulicz's syndrome (affecting the salivary and lacrimal glands)

Küttner's tumor (affecting the submandibular glands)

Riedel's thyroiditis

Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)

Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)

Inflammatory pseudotumor (affecting the orbits, lungs, kidneys, and other organs)

Mediastinal fibrosis

Retroperitoneal fibrosis (Ormond's disease)

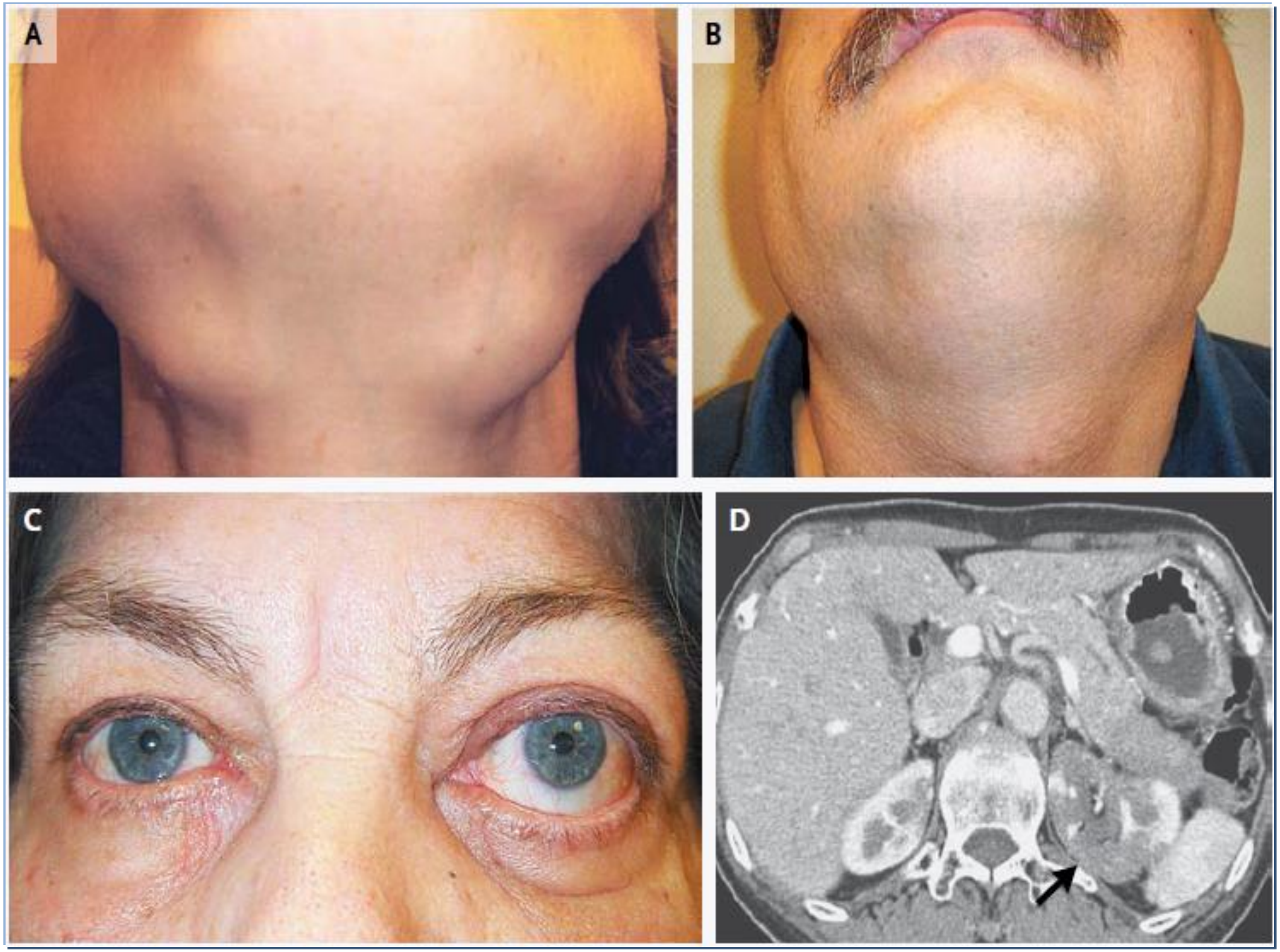
Periaortitis and periarteritis

Inflammatory aortic aneurysm

Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits

(Stone et al, N Engl J Med 2012)

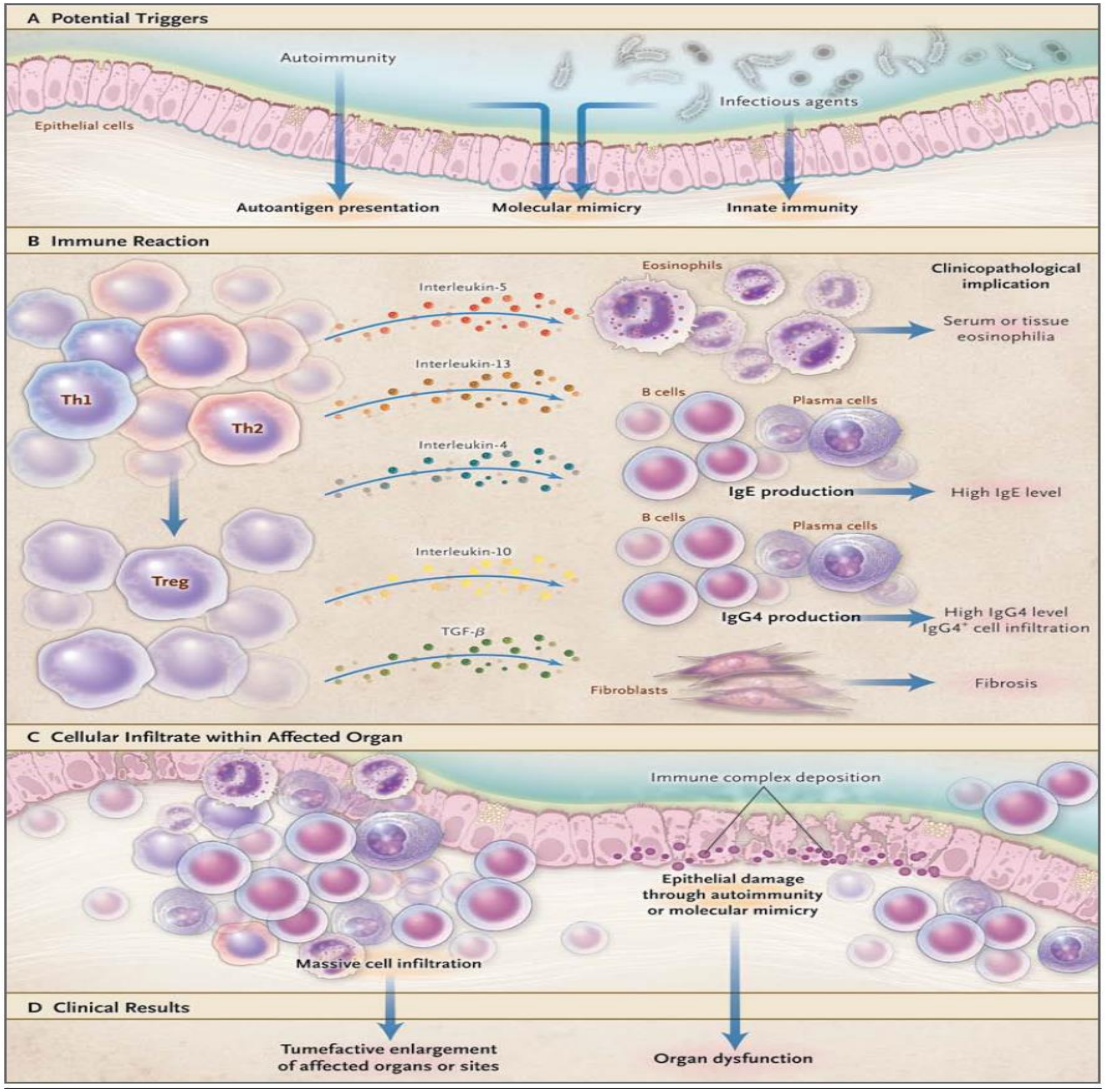
IgG4-RD (3)



(Stone et al, N Engl J Med 2012)

IgG4-RD - Pathogénie

Prolifération clonale des LB IgG4+
(Maillette et al, Hepatology 2013)


A Potential Triggers
Autoimmunity
Infectious agents
Epithelial cells
Autoantigen presentation
Molecular mimicry
Innate immunity
B Immune Reaction
Th1
Th2
Treg
Interleukin-5
Interleukin-13
Interleukin-4
Interleukin-10
TGF-β
Eosinophils
Clinicopathological implication
Serum or tissue eosinophilia
B cells
Plasma cells
IgE production
High IgE level
B cells
Plasma cells
IgG4 production
High IgG4 level
IgG4+ cell infiltration
Fibroblasts
Fibrosis
C Cellular Infiltrate within Affected Organ
Immune complex deposition
Epithelial damage through autoimmunity or molecular mimicry
Massive cell infiltration
D Clinical Results
Tumefactive enlargement of affected organs or sites
Organ dysfunction

Stimulation antigénique chronique ?
« blue collar work»
(Maillette et al, Hepatology 2014)

Rôle précis des IgG4 ?
(Production sous contrôle des Th2)
Rôle anti-inflammatoire ?
(Ag cible : Annexin A11 ?)
(Hubers et al, Gut 2017)

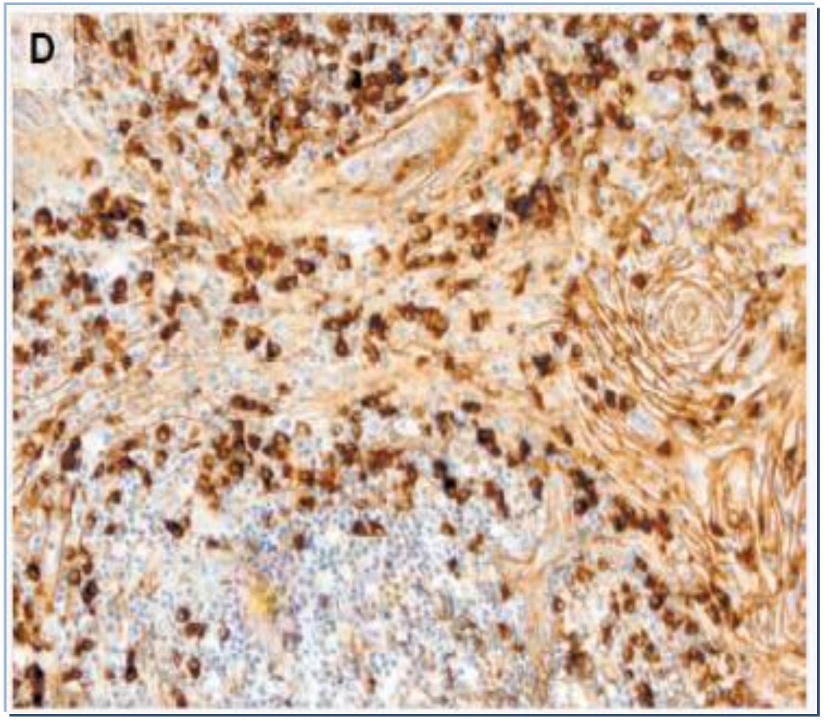
Pathogénie autoimmune ??

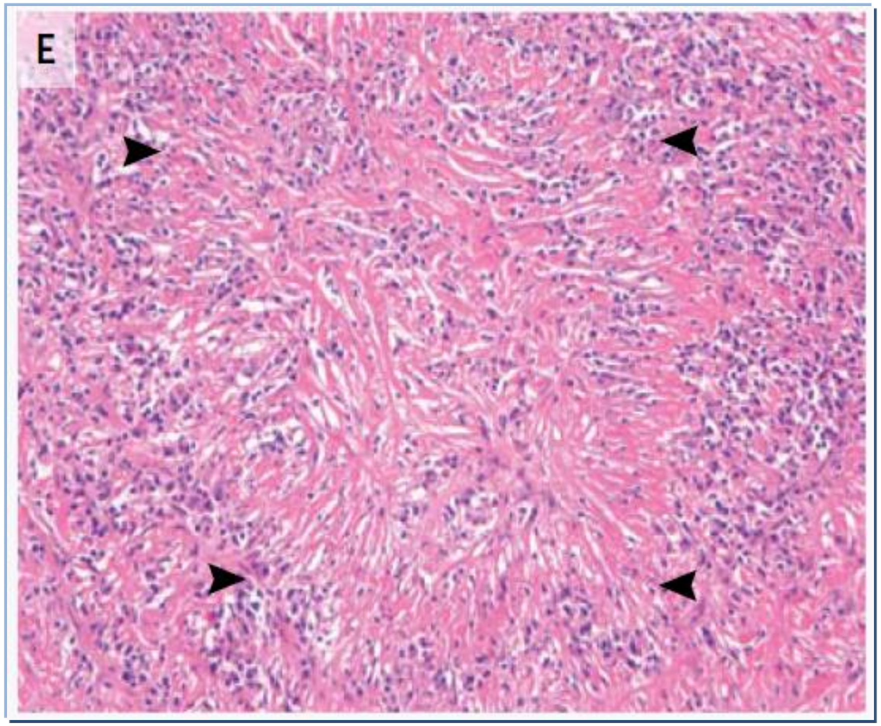
(Stone et al, N Engl J Med 2012)

IgG4: Trois Lésions Histologiques (1)

Inflammation LymphoPlasmocytaire (IgG4+)

Phlébite oblitérante

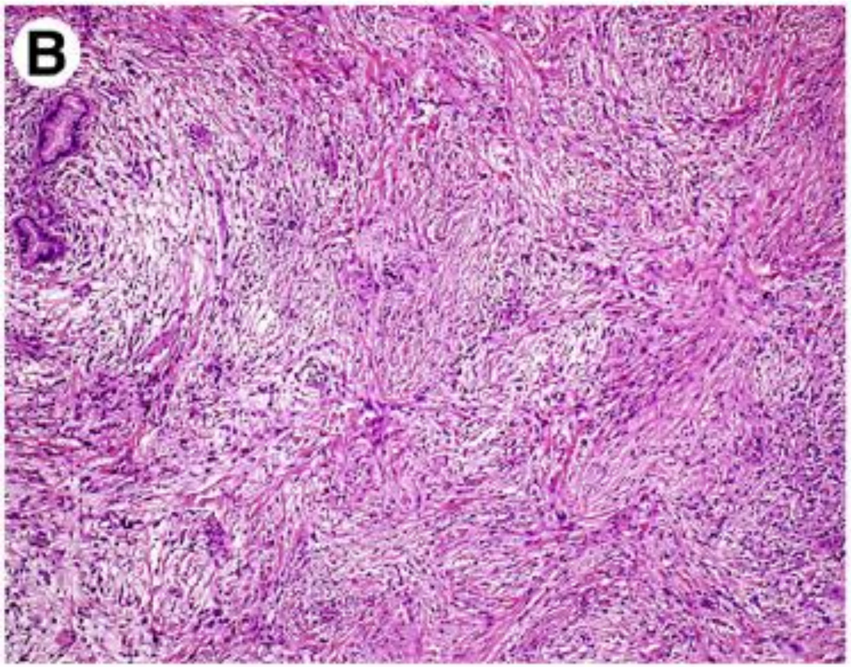


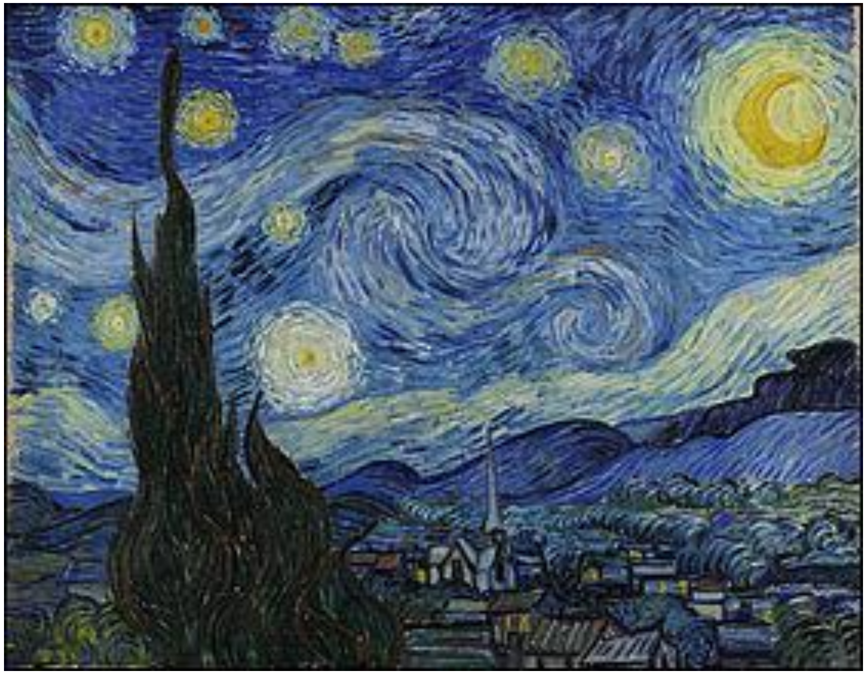


(Stone et al, N Engl J Med 2012)

IgG4: Trois Lésions Histologiques (2)

« Storiform Fibrosis »





(Graham et al, Hum Pathol 2014)

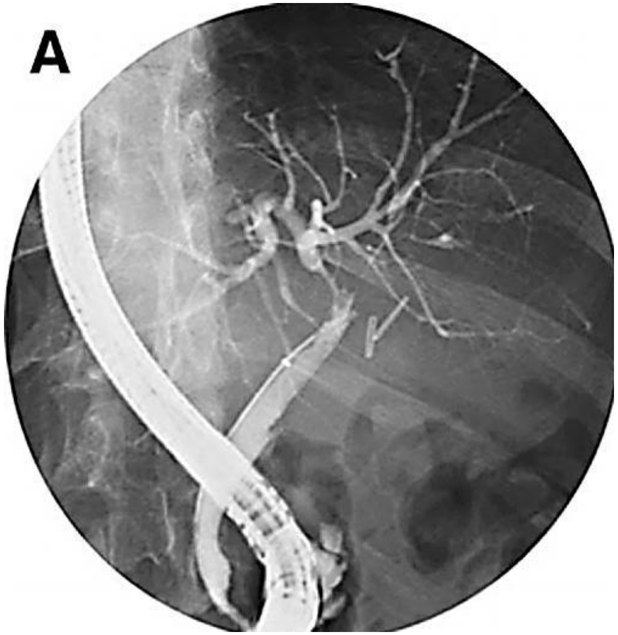
(Vincent Van Gogh, 1889)

« Définition » des Cholangites à IgG4

Maladie sténosante des voies biliaires
caractérisée typiquement par :

- **⇑ IgG4 sériques (>1,4 g/L) (grandes variations physiologiques: 0,01 à 1,4 g/L)**
- **Infiltration des voies biliaires par plasmocytes IgG4**
- **Touchant souvent les voies biliaires extra-hépatiques**
- **Souvent associée à une autre pathologie fibroinflammatoire (IgG4-RD, pancréatite auto-immune [PAI] de type I +++: prévalence au japon = 2,2 à 4,6/10^5)**
- **Prévalence: non connue (15% des PAI I, Beaujon)**
- **Répondant aux corticoïdes**

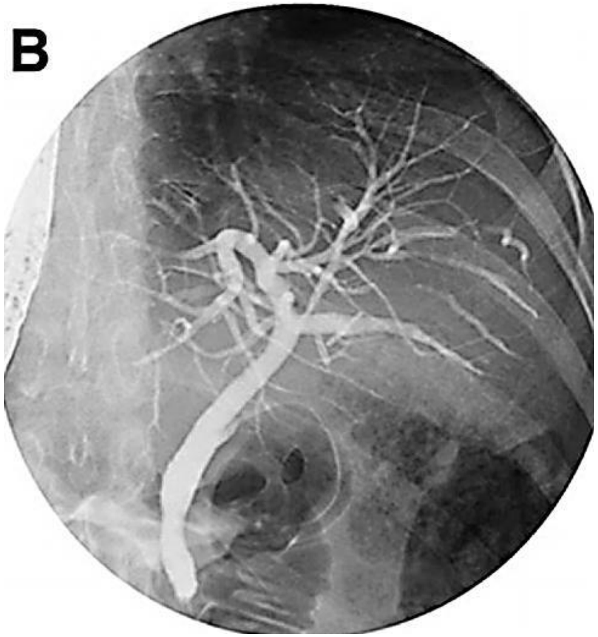
Cholangite à IgG4: Réponse aux Corticoïdes



Prednisone

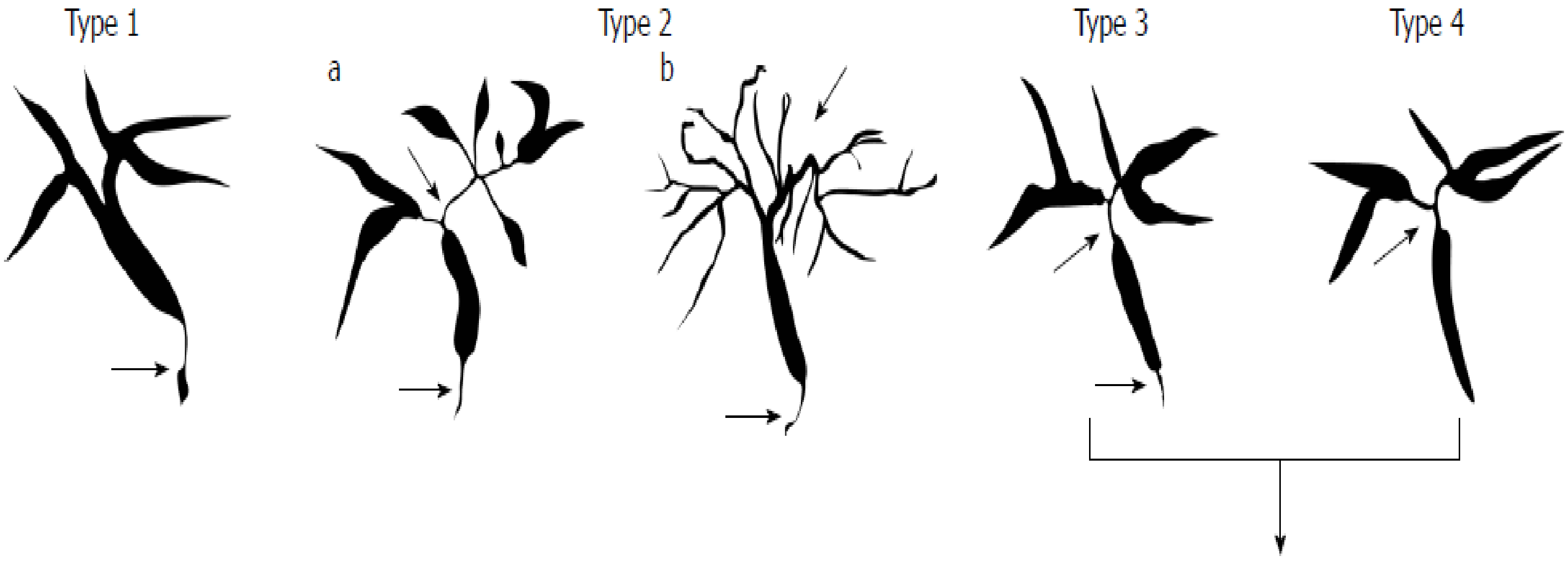
→

12 semaines



(Ghazale et al, Gastroenterology 2008)

IAC: Aspects Cholangiographiques



Differential diagnosis	Pancreatic cancer Bile duct cancer Chronic pancreatitis	Primary sclerosing cholangitis	Bile duct cancer Gallbladder cancer

(Nakazawa et al, World J Gastroenterol 2013)

Atteinte souvent distale, longue

Épaississement circulaire et symétrique de la paroi biliaire

Bien regarder le pancréas (PAI ?)

Cholangite à IgG4 vs CSP

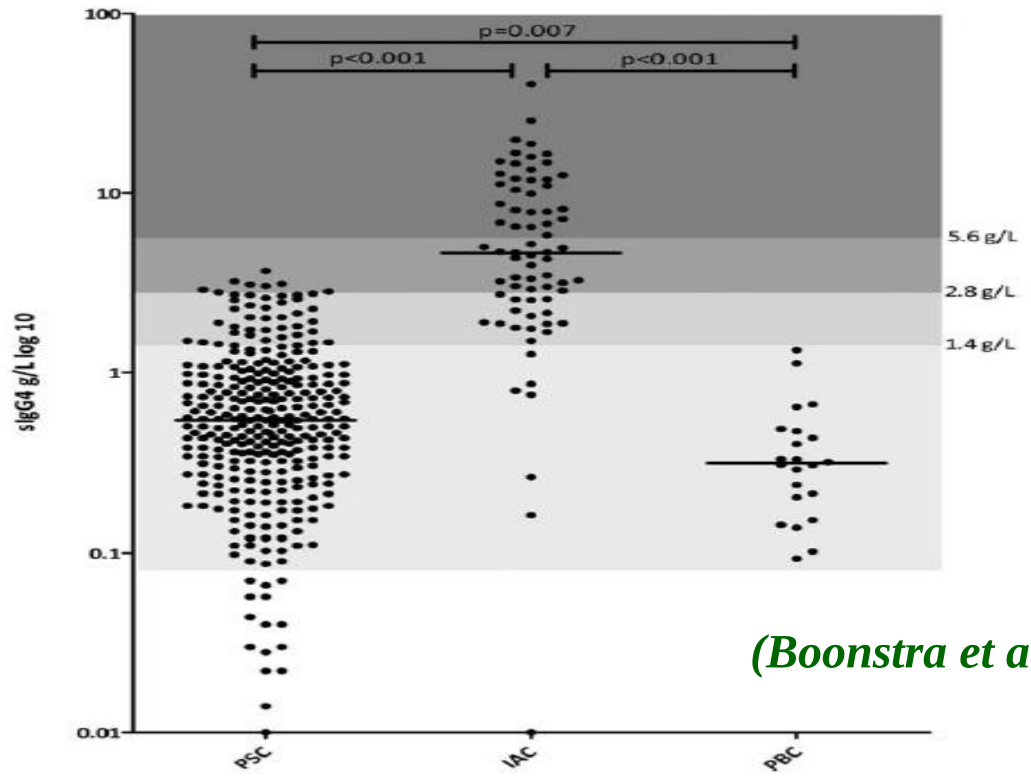
	PSC	IAC
M:F	**2:1**	**8:1**
Age at diagnosis (years)	**25-45**	**65 (jaundice ++)**
Associated with IBD	+++	+
Associated pancreatic dis.	+/-	+++
Associated cholangioca	++	-
Other organ involvement	-	+++
Cholangiographic findings	**Beading. Band-like strictures**	**Segmental and distal bile duct strictures**
Elevated serum IgG4	**7-15%**	**~70%**
IgG4+ plasma cell infiltrate	+/-	++
Response to steroids	-	++

(Webster, EASL 2011)

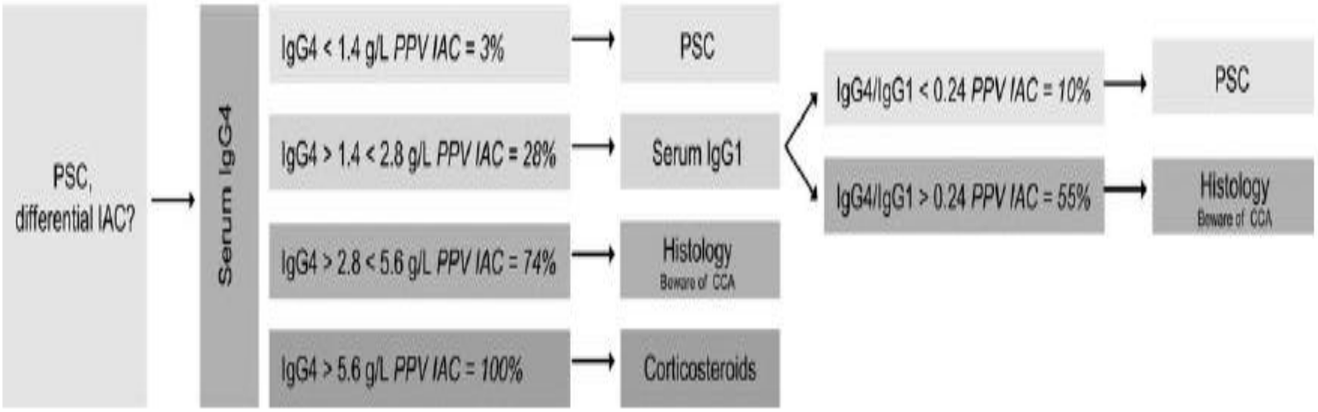
Dosage systématique IgG4 sériques au diagnostic de « CSP »

(AASLD Practice Guidelines, Hepatology 2010)

CSP «Classique » et IgG4



(Boonstra et al, Hepatology 2014)

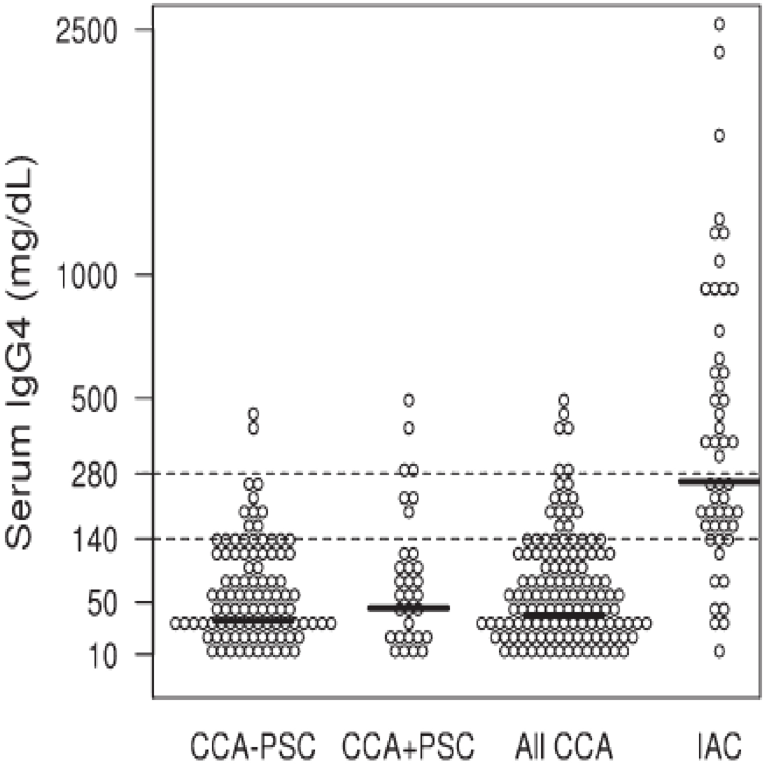


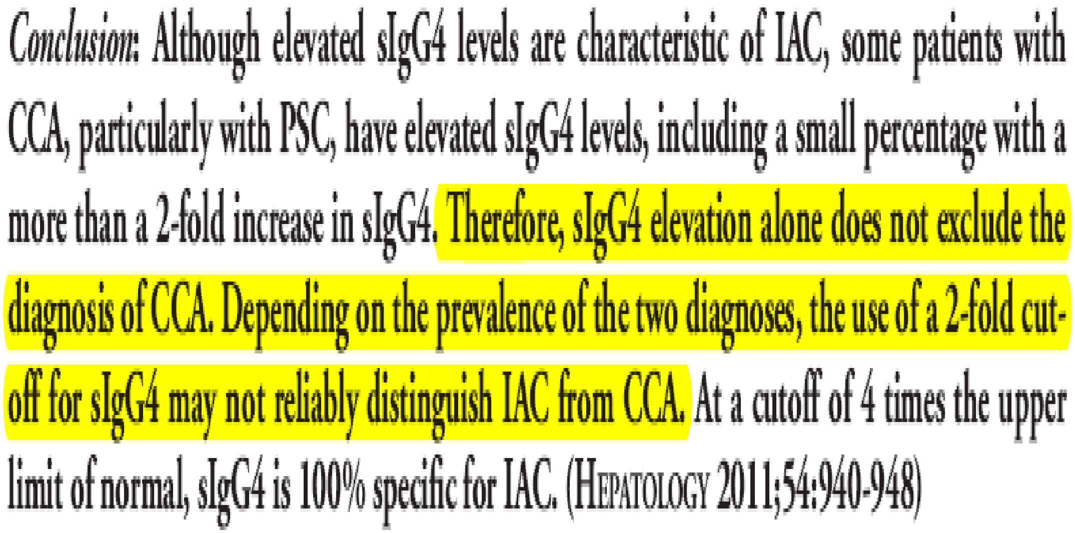
PSC, differential IAC? → Serum IgG4

- IgG4 < 1.4 g/L *PPV IAC = 3%* → PSC
- IgG4 > 1.4 < 2.8 g/L *PPV IAC = 28%* → Serum IgG1
  - IgG4/IgG1 < 0.24 *PPV IAC = 10%* → PSC
  - IgG4/IgG1 > 0.24 *PPV IAC = 55%* → Histology Beware of CCA
- IgG4 > 2.8 < 5.6 g/L *PPV IAC = 74%* → Histology Beware of CCA
- IgG4 > 5.6 g/L *PPV IAC = 100%* → Corticosteroids

Utility of Serum Immunoglobulin G4 in Distinguishing Immunoglobulin G4-Associated Cholangitis from Cholangiocarcinoma

(Hepatology 2011,54:940-948)

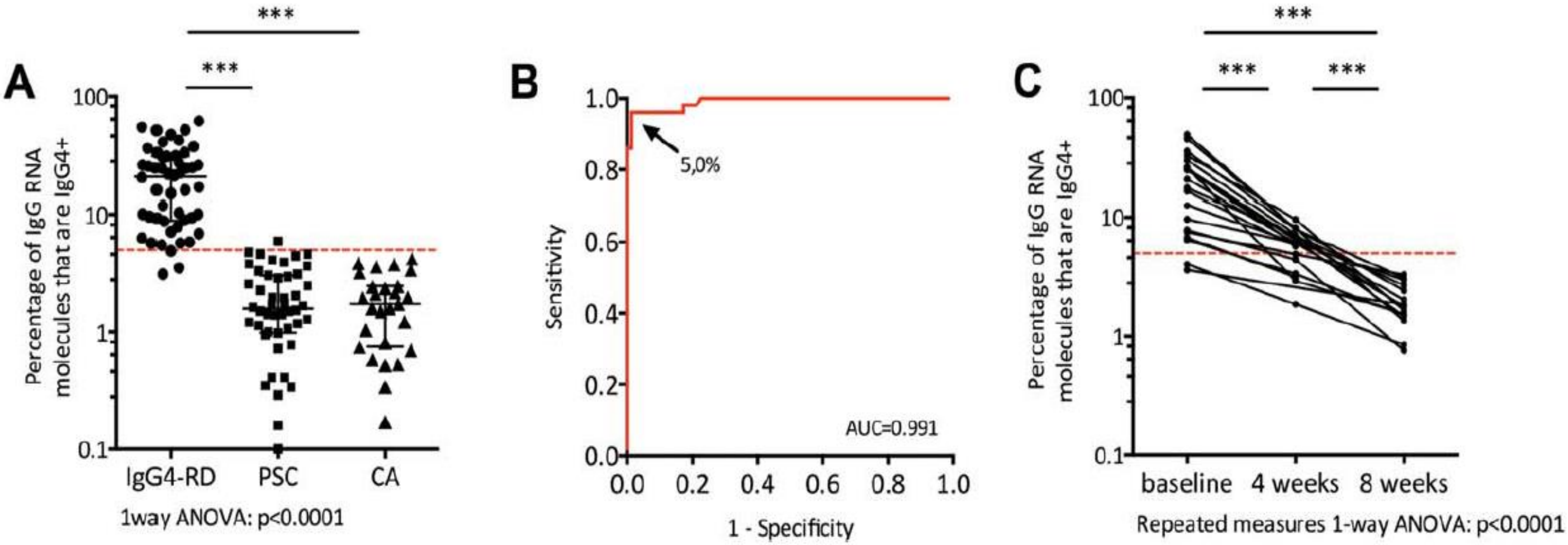




Conclusion: Although elevated sIgG4 levels are characteristic of IAC, some patients with CCA, particularly with PSC, have elevated sIgG4 levels, including a small percentage with a more than a 2-fold increase in sIgG4. Therefore, sIgG4 elevation alone does not exclude the diagnosis of CCA. Depending on the prevalence of the two diagnoses, the use of a 2-fold cut-off for sIgG4 may not reliably distinguish IAC from CCA. At a cutoff of 4 times the upper limit of normal, sIgG4 is 100% specific for IAC. (HEPATOLOGY 2011;54:940-948)

En général: une élévation isolée des IgG4
ne fait pas un diagnostic de cholangite à IgG4…

Rapport IgG4/IgG RNA (récepteur des lymphos B) qPCR



Rapport IgG4/IgG RNA qPCR ≥ 5% vs IgG4 ≥ 1,4 g/L:
sensibilité: 94 vs 86%; spécificité: 99 vs 73%

(Doorenspleet et a1, Hepatology 2016)

Cholangite à IgG4 – Histologie

- **Biopsies endobiliaires: plasmocytes IgG4 (> 10/HPF: 88% ?) mais aucun diagnostic ferme** *(Ghazale et al, Gastroenterology 2008)*

- **Biopsie hépatique:**
  - **Aspects variables, le plus souvent non spécifiques**
  - **Plasmocytes IgG4 (?) (fréquent au Japon)**
  - **Cholangite IgG4: 26% (?), intérêt si sténoses intra-hep ?**

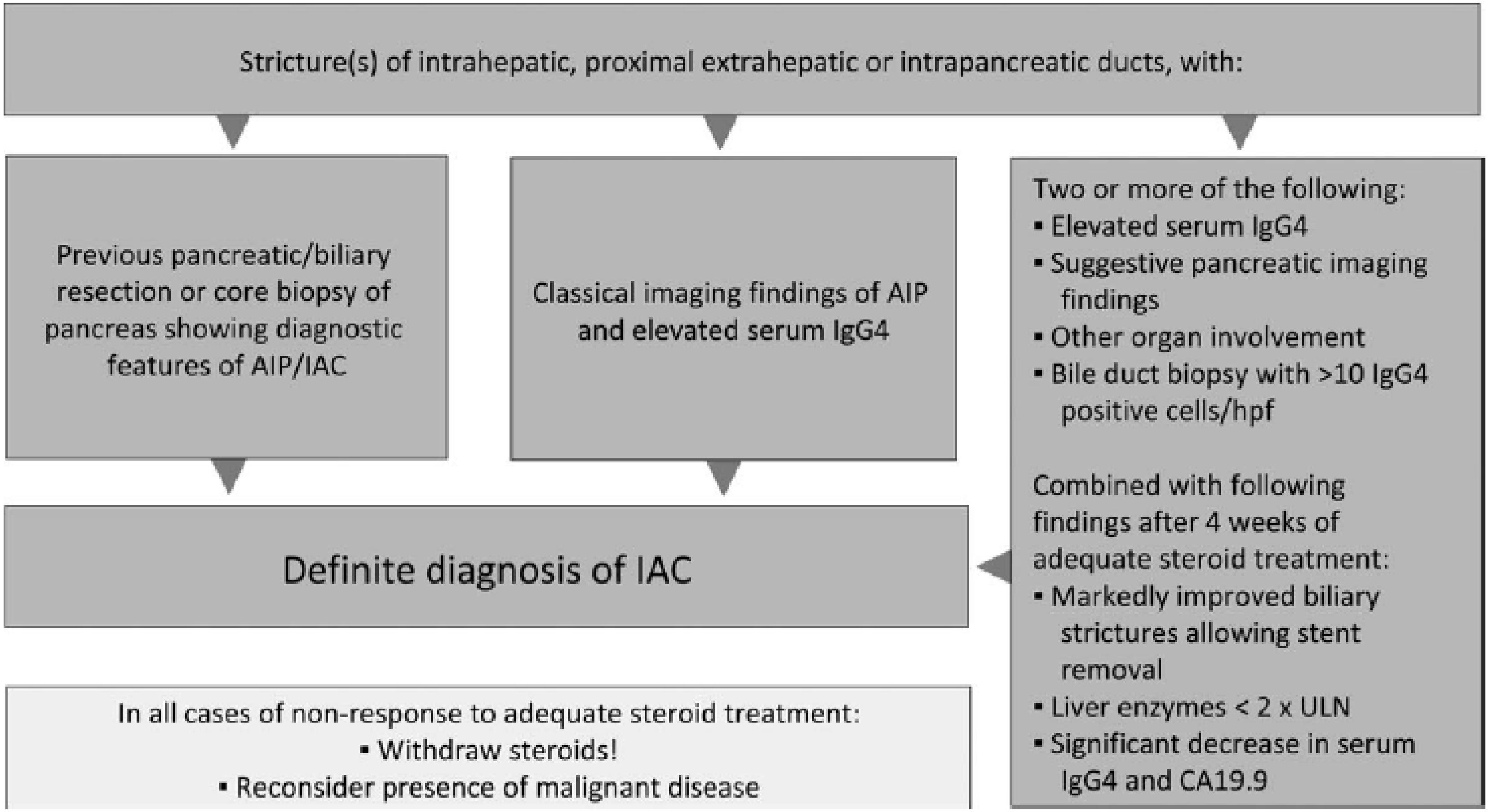
    (Naitoh et al, J.Gastroenterol 2011)

- **Intérêt biopsie endoscopique de la (peri) papille (80% IgG4+ dans PAI) ?** *(Kamisawa et al, Gastrointest Endosc 2008)*

- **IgG4+/IgG+ > 40% +++**

- **(aspect de la muqueuse en cholangioscopie ?)**

Diagnostic IAC: Critères HISORt



Stricture(s) of intrahepatic, proximal extrahepatic or intrapancreatic ducts, with:

Previous pancreatic/biliary resection or core biopsy of pancreas showing diagnostic features of AIP/IAC

Classical imaging findings of AIP and elevated serum IgG4

Two or more of the following:

- Elevated serum IgG4
- Suggestive pancreatic imaging findings
- Other organ involvement
- Bile duct biopsy with >10 IgG4 positive cells/hpf

Combined with following findings after 4 weeks of adequate steroid treatment:

- Markedly improved biliary strictures allowing stent removal
- Liver enzymes < 2 x ULN
- Significant decrease in serum IgG4 and CA19.9

Definite diagnosis of IAC

In all cases of non-response to adequate steroid treatment:

- Withdraw steroids!
- Reconsider presence of malignant disease

. HISORt diagnostic criteria (histology, imaging, serology, other organ involvement, and response to therapy) for IgG4-associated

(Ghazale et al, Gastroenterology 2008)

Poids différents des critères: 1) histo 2) imagerie 3) IgG4 sériques

Cholangite à IgG4 isolée: Diagnostic très difficile !

9 cas de cholangite à IgG4 isolée:

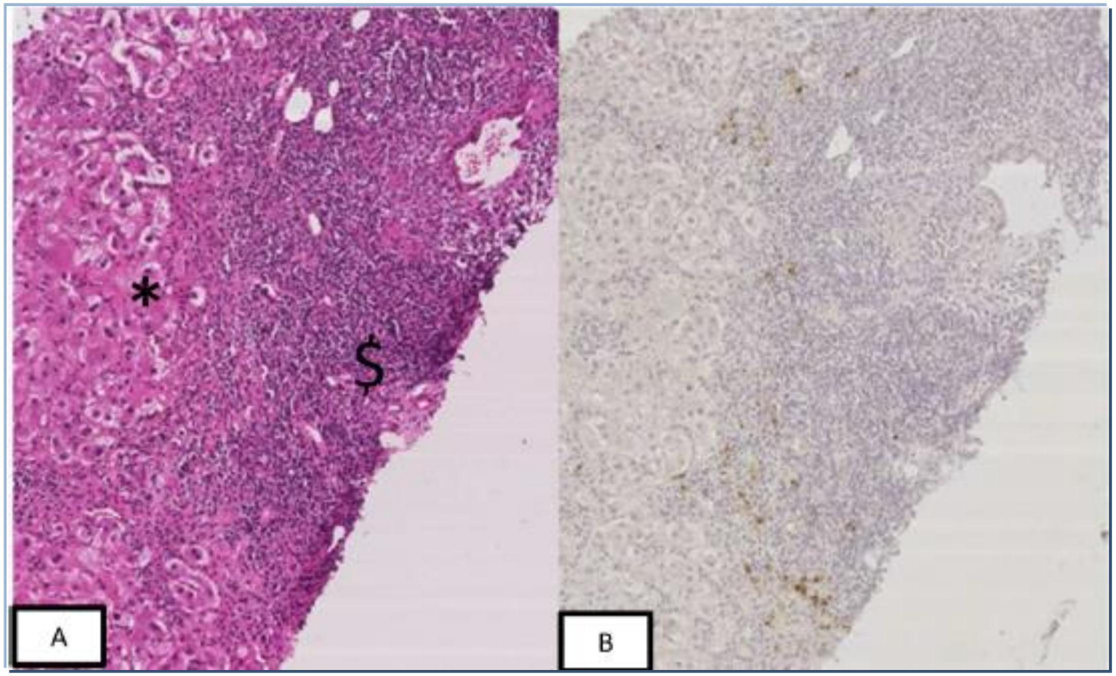
- **Aspect de cholangiocarcinome convergence et VBP**
- **↑ IgG4 (< 2N): 3/8**
- **Résection: 8/9**

(Graham et al, Hum Pathol 2014)

HAI à IgG4 (?)

"Despite anecdotal reports from Japan, confirmation is lacking. Therefore it is difficult to judge, if an entity of AIH-like IgG4 disease exists and presents a separate disease entity."

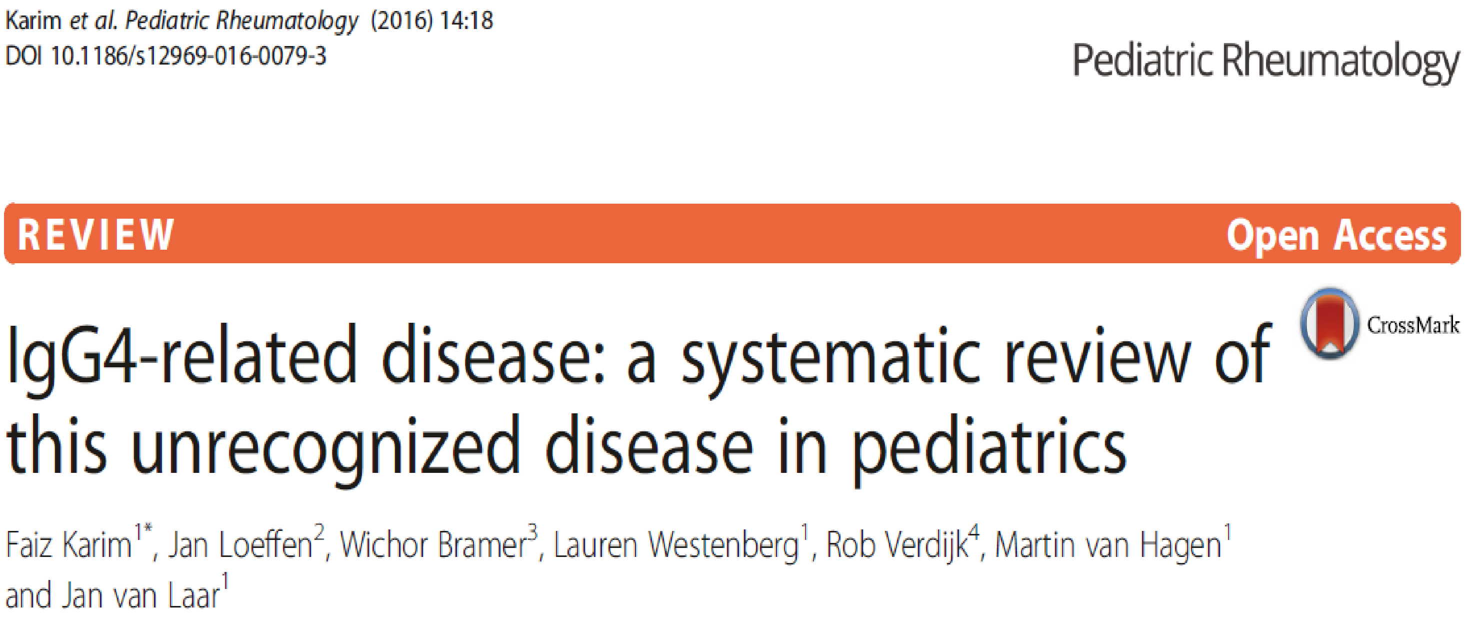
(EASL, Practice Guidelines, J Hepatol 2015)



7/28 HAI
Déf purement histologique
Réponse au Tt: identique

(Canivet et al, Dig Liv Dis 2016)

IgG4-RD et Enfants



Karim *et al. Pediatric Rheumatology* (2016) 14:18
DOI 10.1186/s12969-016-0079-3

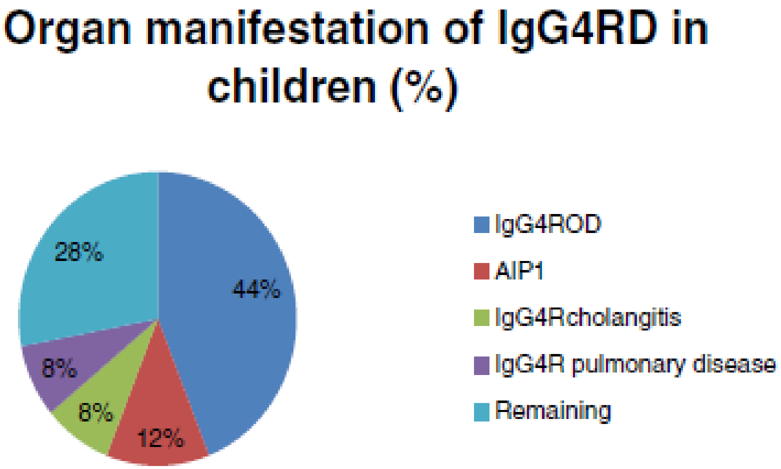
Pediatric Rheumatology

REVIEW **Open Access**

IgG4-related disease: a systematic review of this unrecognized disease in pediatrics

Faiz Karim[1*], Jan Loeffen[2], Wichor Bramer[3], Lauren Westenberg[1], Rob Verdijk[4], Martin van Hagen[1] and Jan van Laar[1]

25 cas (22 case reports)



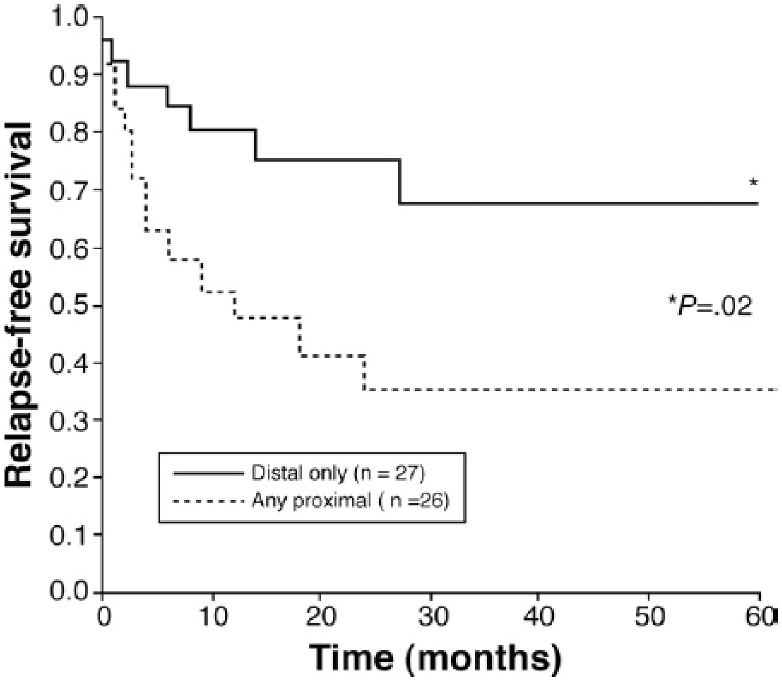
Organ manifestation of IgG4RD in children (%)

Cholangite à IgG4 : Traitement – Evolution (1)

- **Traitement : corticoïdes +++**
  - **Protocole mal codifié :**

    30-40 mg/j pendant 1 mois puis diminution sur 3 mois
  - **Retour à la (quasi) normale des voies biliaires**
  - **Amélioration biologique**
  - **Récidive fréquente (≈ 50%) à l'arrêt du traitement:**

NB: amélioration spontanée possible ! (< 10%)



(Ghazale et al, Gastroenterology 2008)

▸ **azathioprine (2-2,5 mg/kg/j)**

[mycophenolate: 2g/j]

ou

▸ **steroïdes (< 10 mg/j)**

au long cours ?

Cholangite à IgG4 : Traitement – Evolution (2)

- **Résistance:**
  - **Prothèse biliaire**
  - **Rituximab (anti-CD20)**

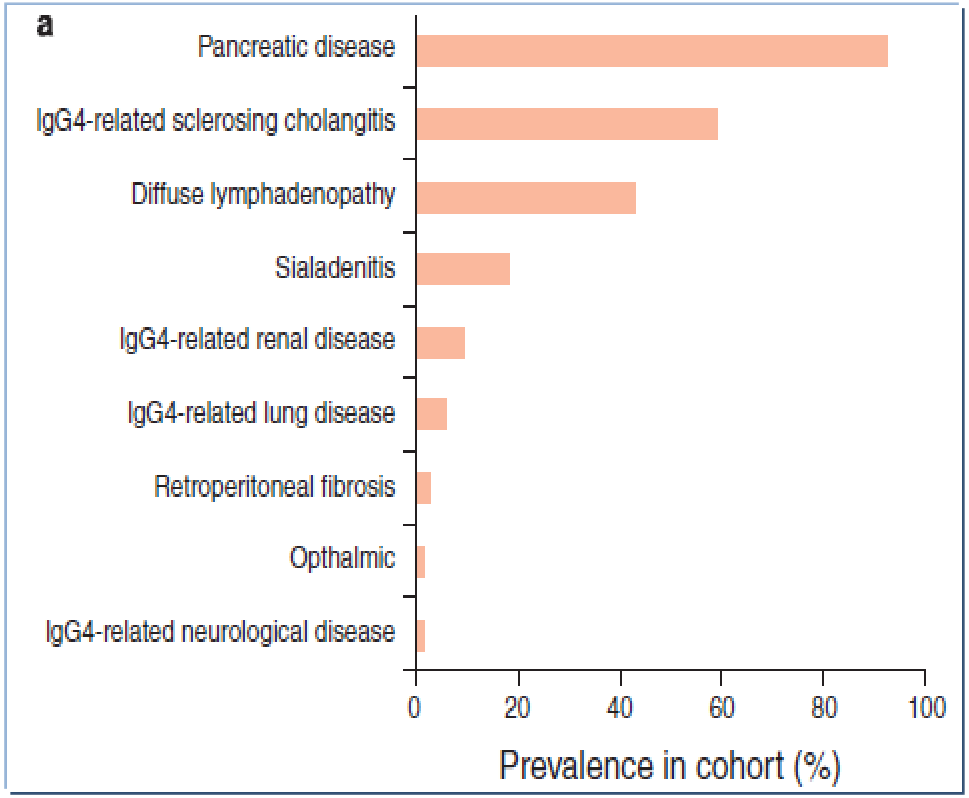
(Topazian et al, Clin Gastroenterol Hepatol 2008)

- **Pronostic à long terme : mal connu**
  - **Amélioration spontanée possible**
  - **Cholangiocarcinome (?)**

(Douhara et al, World J Gastrointest Oncol 2013)

Cholangite à IgG4 : Traitement – Evolution (3)

115 patients avec maladie IgG4, suivi médian : 33 mois



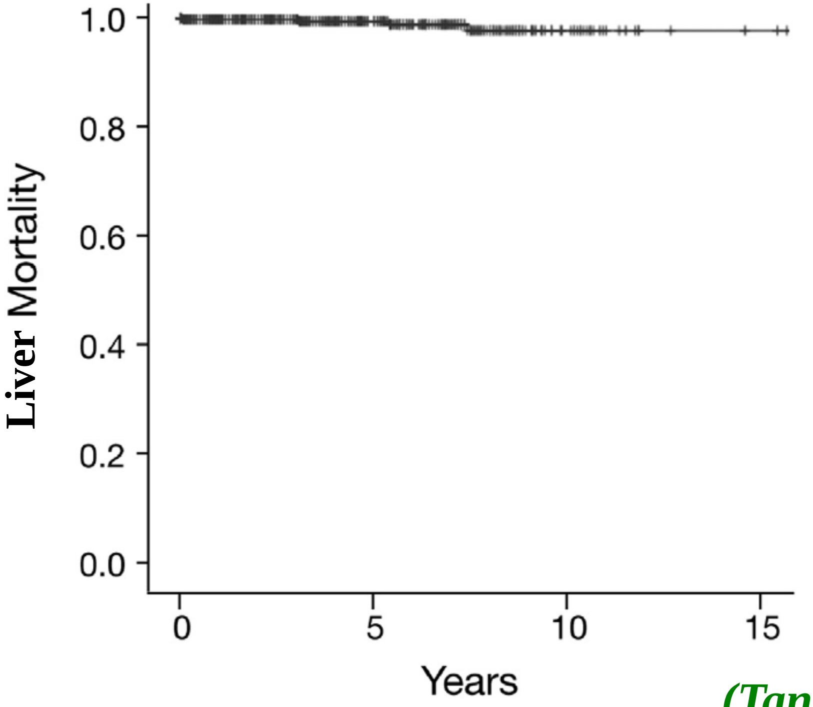
Réponse initiale: 97%
Rechute: 50%

Mortalité: 10% (OR ~ 2)
Cancer: 11% (2 CCA,
+ pancréas, prostate, colon…)
(OR ~ 2)

(Huggett et al, Am J Gastroenterol 2014)

Cholangite à IgG4: Expérience Japonaise

- **Etude rétrospective sur 15 ans, 527 patients !**
- **Age moyen: 66 ans**
- **↑ IgG4: 84%, 87% avec PAI**
- **Survie à 1à ans: 81%**
- **Cholangiocarcinome: 4 (0,8%) (suivi médian 4 ans)**



Réponse aux corticoides: 90%
Récidive sténose biliaire: 19%

(Tanaka et al, Clin Gastroenterol Hepatol 2017)

Pancréatite à IgG4 : Rituximab

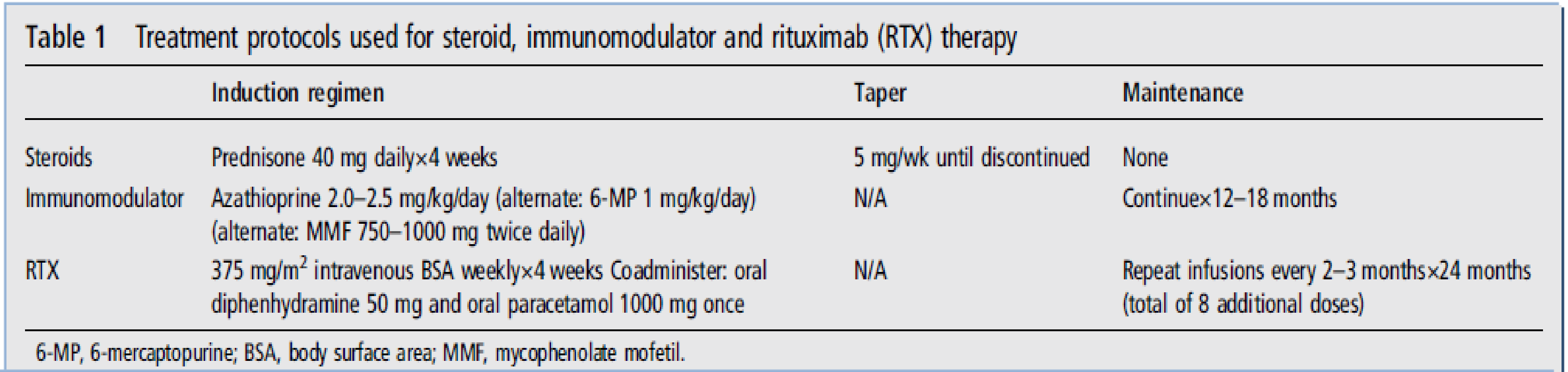


Table 1 Treatment protocols used for steroid, immunomodulator and rituximab (RTX) therapy

	Induction regimen	Taper	Maintenance
Steroids	Prednisone 40 mg daily×4 weeks	5 mg/wk until discontinued	None
Immunomodulator	Azathioprine 2.0–2.5 mg/kg/day (alternate: 6-MP 1 mg/kg/day) (alternate: MMF 750–1000 mg twice daily)	N/A	Continue×12–18 months
RTX	375 mg/m^2 intravenous BSA weekly×4 weeks Coadminister: oral diphenhydramine 50 mg and oral paracetamol 1000 mg once	N/A	Repeat infusions every 2–3 months×24 months (total of 8 additional doses)

6-MP, 6-mercaptopurine; BSA, body surface area; MMF, mycophenolate mofetil.

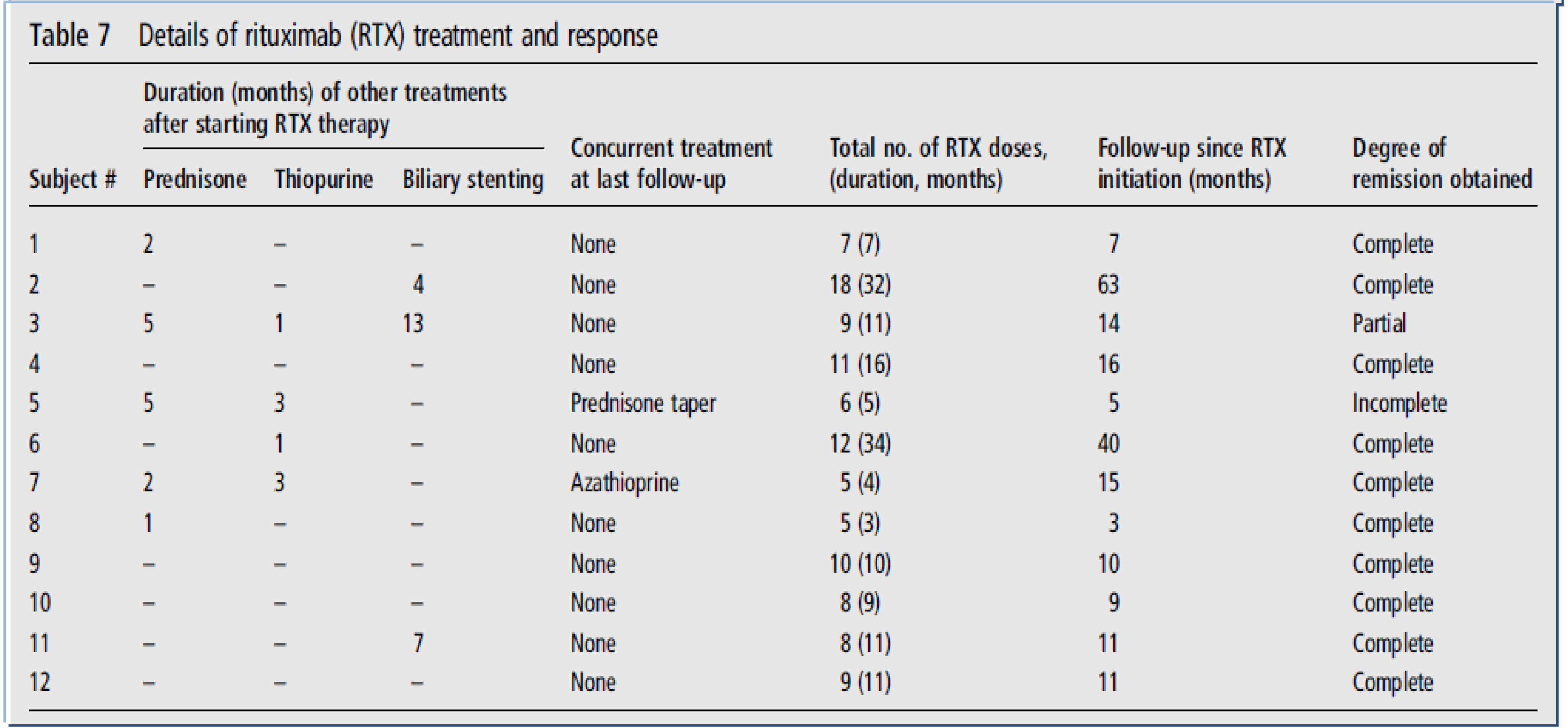


Table 7 Details of rituximab (RTX) treatment and response

	Duration (months) of other treatments after starting RTX therapy						
Subject #	Prednisone	Thiopurine	Biliary stenting	Concurrent treatment at last follow-up	Total no. of RTX doses, (duration, months)	Follow-up since RTX initiation (months)	Degree of remission obtained
1	2	–	–	None	7 (7)	7	Complete
2	–	–	4	None	18 (32)	63	Complete
3	5	1	13	None	9 (11)	14	Partial
4	–	–	–	None	11 (16)	16	Complete
5	5	3	–	Prednisone taper	6 (5)	5	Incomplete
6	–	1	–	None	12 (34)	40	Complete
7	2	3	–	Azathioprine	5 (4)	15	Complete
8	1	–	–	None	5 (3)	3	Complete
9	–	–	–	None	10 (10)	10	Complete
10	–	–	–	None	8 (9)	9	Complete
11	–	–	7	None	8 (11)	11	Complete
12	–	–	–	None	9 (11)	11	Complete

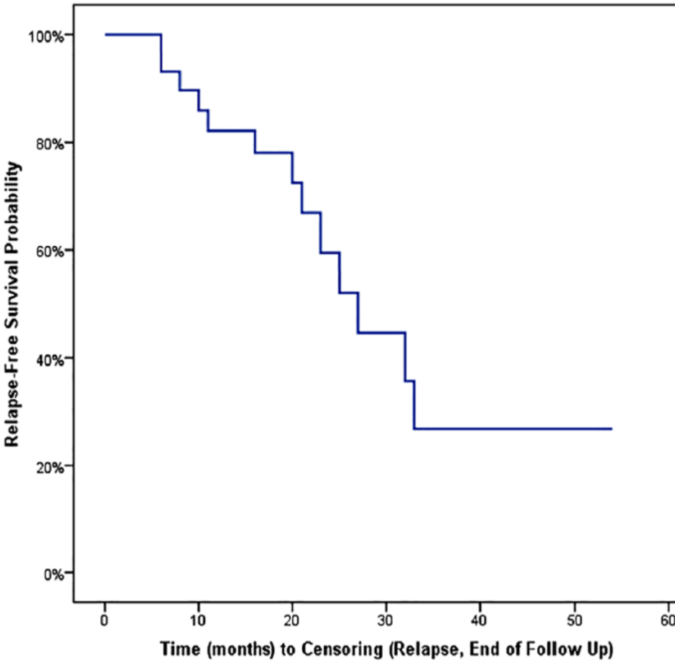
(Hart et al, Gut 2013)

IgG4-RD: Expérience Française Rituximab

Table 3. Clinical, biological and radiological efficacy of RTX in 33 patients with IgG4-RD. (13 avec atteinte biliaire)

(Ebbo el al, PlosOne 2017)

Outcome	**n (%)**
RTX regimen	
1 g d1-d15	25 (75.8)
375 mg/m²/w x4	6 (18.2)
Other	2 (6.1)
Clinical response[a]	29/31 (93.5)
Biological response on serum IgG4[b]	
Serum IgG4 decrease >50%	16/19 (84.2)
Serum IgG4 normalization (<135 mg/dl)	14/19 (73.7)
Biological response on non-specific biology[c]	21/23 (91.3)
Radiological response (conventional, CT or MRI)	
Radiological stabilization	5/13 (38.5)
Radiological improvement	4/13 (30.75)
Radiological normalization	4/13 (30.75)
Metabolic response (FDG-PET/CT)	
No metabolic response/worsening	1/14 (7.1)
Metabolic stabilization	3/14 (21.4)
Metabolic improvement	4/14 (28.6)
Metabolic normalization	6/14 (42.9)
Glucocorticoid withdrawal[d]	17/33 (51.5)
DMARD treatment[d]	6/33 (18.2)
Mean follow-up, months (±SD)	24.8 (±21.0)
Relapse[e]	13/31 (41.9)
Mean time to relapse, months (±SD)	19.0 (±11.5)
Retreatment with RTX	17/33 (51.5)
Systematic/maintenance retreatment[f]	12/33 (36.4)
Retreatment for relapse[f]	9/33 (27.2)



Infections sévères :
4 patients

Cholangite à IgG4 - Conclusions

- **Encore beaucoup d'inconnues (et de pièges)**

- **En pratique devant une « cholangite sclérosante » y penser :**
  - **Toujours et encore plus si: pathologie pancréatique, homme, âge > 60 ans, ictère brutal, absence de MICI**

- **Critères HISORt…mais histo rarement formelle (hors chir) et [IgG4] pas tjs ↑ → probabilité plus que certitude**

- **Traitement: corticoïdes (si arguments diagnostiques forts)**
  - **Récidive fréquente**
  - **Rituximab ?**