IgG4-related Disease: An underrecognized entity

Michael Trauner, M.D.
Division of Gastroenterology & Hepatology & Intensive Care Unit 13H1
Department of Internal Medicine III
IgG4-related Disease: An increasingly recognized entity

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Disclosures

• Speakers bureau
  – Falk Foundation, Gilead, MSD, Roche

• Advisor
  – Albireo, Falk, Genfit, Intercept, MSD, Novartis, Phenex

• Travel grants
  – Falk Foundation, Gilead, Roche

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  – Albireo, Falk Pharma, Gilead, Intercept, MSD, Takeda

• Property rights
  – The Medical University of Graz has filed patents on the medical use of norUDCA and I am listed as co-inventor
IgG4-related Disease (IgG4-RD)
IgG4-related disease

Orbit
- Orbital inflammatory pseudotumor (IgG4-related pan-orbital inflammation)

Central nervous system
- Hypertrophic pachymeningitis
- Hypophysitis

Salivary and lacrimal glands
- Sclerosing sialadenitis and dacrooadenitis
- Kütter tumor (isolated submandibular gland involvement)
- Mikulicz disease (simultaneous salivary and lacrimal gland involvement)

Lymph nodes
- IgG4-related lymphadenopathy

Pancreas and biliary tract
- Type I autoimmune pancreatitis
- IgG4-related hepatopathy
- Sclerosing cholangitis
- Cholecystitis

Thyroid
- Riedel thyroiditis (fibrous thyroiditis)

Retroperitoneum
- Ormond disease (idiopathic retroperitoneal fibrosis)
- Inflammatory aortic aneurysm (inflammatory aortitis/aortic dissection)

Mediastinum
- Fibrosing mediastinitis
- Inflammatory aortic aneurysm (inflammatory aortitis/aortic dissection)
- IgG4-related lung disease/pleuritis
- IgG4-related pericarditis

Genitourinary tract
- Ureteral obstruction with hydrenephrosis
- Tubulointerstitial nephritis
- Membranous glomerulonephritis
- Prostatitis
# IgG4-related disease of the bile ducts and pancreas

## Background

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Title</th>
<th>Journal, Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Erkelens et al.</td>
<td>Sclerosing pancreato-cholangitis responsive to steroid therapy</td>
<td>Lancet 354:43</td>
</tr>
<tr>
<td>2003</td>
<td>Kamisawa et al.</td>
<td>IgG4-related systemic disease</td>
<td>J Gastroenterol 38:982</td>
</tr>
</tbody>
</table>
Panel 1: Conditions once regarded as individual disorders now recognised to be part of IgG4-related disease

- Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
- Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
- Fibrosing mediastinitis
- Hypertrophic pachymeningitis
- Idiopathic hypocomplementaemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
- Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs)
- Küttner’s tumour (affecting the submandibular glands)
- Mikulicz’s disease (affecting the salivary and lacrimal glands)
- Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
- Periaortitis and periarteritis
- Inflammatory aortic aneurysm
- Retroperitoneal fibrosis (Ormond’s disease)
- Riedel’s thyroiditis
- Sclerosing mesenteritis

IgG4-related disease

Lancet 2015; 385: 1460–71
Terumi Kamisawa, Yoh Zen, Shiv Pillai, John H Stone
IgG4-related Disease - Pubmed

Nationwide population survey (Japan)
2007 → 2011
Incidence 0.9 → 1.4 per 100,000
Prevalence 2.2 → 4.6 per 100,000

Weindorf & Fredriksen, Arch Pathol Lab Med 2017; 141: 1476-83
IgG4-related Disease - Worldwide

Slide Courtesy B. Eksteen, Alberta
## IgG4-related Disease (IgG4-RD)

<table>
<thead>
<tr>
<th>Abdominal and pelvic localisation</th>
<th>Extra-abdominal IRD localisation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bile ducts (IAC), gallbladder and liver</strong></td>
<td>Hypophysis</td>
</tr>
<tr>
<td><strong>Pancreas (AIP)</strong></td>
<td>Eye, retro-orbital tumor</td>
</tr>
<tr>
<td><strong>Stomach, intestine, ileal pouch</strong></td>
<td><strong>Salivary and lacrimal glands</strong></td>
</tr>
<tr>
<td><strong>Retroperitoneum</strong></td>
<td><strong>Thyroid gland</strong></td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td>Lungs</td>
</tr>
<tr>
<td><strong>Pseudotumor</strong></td>
<td><strong>Lymphatic system (lung hilus !)</strong></td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td><strong>Vascular system (aortitis)</strong></td>
</tr>
<tr>
<td><strong>Testis</strong></td>
<td></td>
</tr>
</tbody>
</table>
# IgG4-related Disease (UK Experience)

<table>
<thead>
<tr>
<th>Case Details</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>105 cases, prospective 10 yr follow-up, Oxford</td>
<td>74% jaundice</td>
</tr>
<tr>
<td>37% abdominal pain</td>
<td>3% pancreatitis</td>
</tr>
<tr>
<td>21% hepato-biliary surgery</td>
<td>59% PSC-biliary changes</td>
</tr>
<tr>
<td>Median 3 months FU mortality</td>
<td>10%</td>
</tr>
<tr>
<td>97% initial steroid response but 50% relapse rate</td>
<td>10% of PSC cases are IgG4 disease</td>
</tr>
<tr>
<td>Malignancy</td>
<td>11% (any cancer)</td>
</tr>
</tbody>
</table>

**Diagram:**

- Pancreatic disease
- IgG4-related sclerosing cholangitis
- Diffuse lymphadenopathy
- Sialadenitis
- IgG4-related renal disease
- IgG4-related lung disease
- Retroperitoneal fibrosis
- Ophthalmic
- IgG4-related neurological disease

**Prevalence in cohort (%)**

Consensus statement on the pathology of IgG4-related disease

Deshpande et al., Modern Pathology 2012; 25: 1181-1192

- Lymphoplasmocytic infiltration
- Storiform fibrosis
- Obliterative phlebitis
- Open artery
## Consensus statement on the pathology of IgG4-related disease

**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

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Numbers of IgG4+ plasma cells (/hpf)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningus</td>
<td>&gt;10</td>
<td>55</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>&gt;100</td>
<td>28</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>&gt;100</td>
<td>17,34</td>
</tr>
<tr>
<td>Lymph node</td>
<td>&gt;100</td>
<td>27</td>
</tr>
<tr>
<td>Lung (surgical specimen)</td>
<td>&gt;50</td>
<td>10,35</td>
</tr>
<tr>
<td>Lung (biopsy)</td>
<td>&gt;20</td>
<td>10,35</td>
</tr>
<tr>
<td>Plaera</td>
<td>&gt;50</td>
<td>6</td>
</tr>
<tr>
<td>Pancreas (surgical specimen)</td>
<td>&gt;50</td>
<td>30,32</td>
</tr>
<tr>
<td>Pancreas (biopsy)</td>
<td>&gt;10</td>
<td>56,57</td>
</tr>
<tr>
<td>Bile duct (surgical specimen)</td>
<td>&gt;50</td>
<td>49</td>
</tr>
<tr>
<td>Bile duct (biopsy)</td>
<td>&gt;10</td>
<td>58,59</td>
</tr>
<tr>
<td>Liver (surgical specimen)</td>
<td>&gt;50</td>
<td>49</td>
</tr>
<tr>
<td>Liver (biopsy)</td>
<td>&gt;10</td>
<td>12,60</td>
</tr>
<tr>
<td>Kidney (surgical specimen)</td>
<td>&gt;30</td>
<td>15</td>
</tr>
<tr>
<td>Kidney (biopsy)</td>
<td>&gt;10</td>
<td>61</td>
</tr>
<tr>
<td>Aorta</td>
<td>&gt;50</td>
<td>16,51,52</td>
</tr>
<tr>
<td>Retropertoneum</td>
<td>&gt;30</td>
<td>8</td>
</tr>
<tr>
<td>Skin</td>
<td>&gt;200</td>
<td>62,63</td>
</tr>
</tbody>
</table>

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

- Green boxes = Histologically highly suggestive of IgG4-RD

### IgG4+ plasma cells

Deshpande et al., *Modern Pathology* 2012; 25: 1181-92
IgG4-related disease (IgG4-RD)

The typical patient in Gastroenterology & Hepatology

- Male (>80%)
- Middle aged / elderly (> 50 yrs)
- Localized organ swelling / tumor
- Elevated serum / tissue IgG4
- Other organ manifestations of IgG4-related disease (IRD)

After immuno-suppressive therapy:

71 yrs, m; IgG4 11.9 g/L (n < 1.4)
De Buy Wenninger et al., Endoscopy 2012: 44: 66-73
IgG4-related disease (IgG4-RD)

Clinical and radiological features in a typical patient
Spectrum of IgG4 organ involvement on FDG-PET/CT imaging
IgG4-associated cholangitis & pancreatitis

Misdiagnosis common!

Björnsson et al., Hepatology 2007; 45: 1547
## Diagnostic HISORt criteria for IgG4-RD

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| **Histology**     | - Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis  
                   | - Lymphoplasmacytic infiltrate with > 10 IgG4+ plasma cells/HPF           |
| **Pancreatic Imaging** | Typical: diffuse gland enlargement; diffuse attenuated pancreatic duct.  
                   | Others: focal mass/stricture; atrophy; calcification; pancreatitis       |
| **Serology**      | Elevated serum IgG4                                                      |
| **Other organs**  | Biliary strictures; salivary/lacrimal gland enlarged; mediastinal lymphadenopathy; retroperitoneal fibrosis; lung disease; tubulointerstitial nephritis |
| **Response to Steroids** | Resolution/marked improvement of pancreatic/extrapancreatic manifestation |

Role of IgG4 in health and disease

- Important diagnostic marker for IgG4-RD (with pitfalls!)
- Smallest fraction of total IgG in serum
- ‘Regulatory’ antibody, unable to bind C1q, low Fc affinity
- Upregulated in chronic immune stimulation (e.g., allergies)
- Can exchange Fab arm

Slide Courtesy U. Beuers, Amsterdam
van der Neut Kolfschoten et al., Science 2007; 317: 1554
Role of IgG4 in health and disease

Allergies/hypersensitivities
- Advantageous suppression
  - Beekeepers
  - Animal laboratory workers
  - Allergen-specific immunotherapy

Malignancies and Parasitic infections
- Disadvantageous suppression
  - Melanoma and cholangiocarcinoma
  - Helminthic infections

Autoimmune/immune-mediated diseases
- Pathogenic
  - Pemphigus vulgaris and foliaceus
  - MuSK-myasthenia gravis

Slide Courtesy U. Beuers, Amsterdam

Trampert, Hubers, van de Graaf, Beuers. BBA 2018; 1864:1401-1409
IgG4 – bystander or pathogenic?

• Exact role in disease pathogenesis remains uncertain.

• Th2 and regulatory T cell reactions increased in IGg4 related disease when compared with PSC or PBC. This pattern also observed in allergic disorders such as bronchial asthma and atopic dermatitis.

• Also postulated that IgG4 plays no pathogenic role, but that it is upregulated in response to chronic exposure to microbial or non-microbial antigens (eg H pylori).

• Recruitment of IgG4-committed B cells may result from an excessive production of anti-inflammatory cytokines (eg TGF and IL-10) at the site of inflammation.
IgG4-RD

Disease pathways involved in IgG4-RD

A. Initiating mechanisms
   - Infectious agents? (With or without molecular mimicry)
   - Local autoantigen? (Leading to autoimmunity)
   - Allergic component? (Long-term exposure to occupational compounds)
   - Genetic predisposition (HLA and non-HLA genes)

B. Immune reaction
   - Th2 cell predominance
   - ↑ Cytokines: IL-4, IL-5, IL-13
   - iTreg upregulation
     - IL-10 release
     - TGF-β
     - Storiform fibrosis
   - Elevated serum IgE
     - Eosinophilia
   - B cell class switching
     - Increased IgG4 production
   - Direct pathogenic effect?
     - Tissue infiltration by IgG4+ plasma cells
     - High serum IgG4
Clonal expansion of IgG4+ B cells suggests (auto)antigen stimulation

Annexin A11 is the first IgG4 autoantigen identified in IgG4-RD

Hubers et al., Gut 2018; 67(4):728-735
IAC as blue collar worker’s disease

Maillette de Buy Wenniger et al., Hepatology 2014; 60: 1453-4

• Exposure to occupational antigens might predispose to IgG4-related disease
• Majority had a career in blue collar occupations with prolonged exposures to potentially hazardous occupational antigens (pat. history!)
• Chronic antigenic load associated with ‘dirty’ jobs may predispose to IAC (toxin-induced B cell clone expansion?)
• IgG4 may have immunoregulatory function?
Exposure to occupational antigens might predispose to IgG4-related disease

<table>
<thead>
<tr>
<th>Job history of 25 patients from the Amsterdam cohort (&gt; 1 year)</th>
<th>Recalled regular occupational exposures (&gt; 1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Musician, painter, metal worker, carpenter</td>
<td>solvents, car paint, metal, pigments</td>
</tr>
<tr>
<td>2. Carpenter</td>
<td>solvents, sawdust, wood, chipboard</td>
</tr>
<tr>
<td>3. Glass worker, project manager at multinational</td>
<td>glass dust, glass components, lead, barium, cobalt, nickel, lead, silica, industrial dust, butane</td>
</tr>
<tr>
<td>4. Plasterer</td>
<td>solvents, chalk dust, sawdust, wood, chipwood</td>
</tr>
<tr>
<td>5. Industrial warehouse forklift driver</td>
<td>unknown (deceased)</td>
</tr>
<tr>
<td>6. Industrial fuel/waste oil laboratory, skipper</td>
<td>solvents, crude oil, ship waste oil, chemicals</td>
</tr>
<tr>
<td>7. Miner, tiler, bath superintendent</td>
<td>solvents, silica dust, mine dust, asbestos, glue</td>
</tr>
<tr>
<td>8. Metal worker, textile worker</td>
<td>solvents, metal dust, textiles, pigments, paints</td>
</tr>
<tr>
<td>9. Shipping</td>
<td>solvents, asbestos, crude oil</td>
</tr>
<tr>
<td>10. Painter, army officer, flight arrangements, tomato farmer</td>
<td>solvents, paint, pigments, kerosene, pesticides, friction plate dust</td>
</tr>
<tr>
<td>11. Painter</td>
<td>solvents, paint, pigments, dust</td>
</tr>
<tr>
<td>12. Small machine factory owner</td>
<td>solvents, car paint, metal dust, asbestos, oils</td>
</tr>
<tr>
<td>13. Builder, plumber</td>
<td>plumbing materials, dust, sawdust, glue, lead</td>
</tr>
<tr>
<td>14. Self-employed optometrist</td>
<td>lense glass dust, lense plastic dust, acetone</td>
</tr>
<tr>
<td>15. Carpenter</td>
<td>solvents, sawdust, clipboard, glue</td>
</tr>
<tr>
<td>16. Bricklayer, industrial cleaner of house walls</td>
<td>solvents, silica dust, concrete dust, brick dust, asbestos</td>
</tr>
<tr>
<td>17. Mud worker, shipping, mud industry manager</td>
<td>solvents, oil products, dust</td>
</tr>
<tr>
<td>18. Builder, painter</td>
<td>solvents, sawdust, clipboard, paints</td>
</tr>
<tr>
<td>19. Car industry worker</td>
<td>solvents, oil products</td>
</tr>
<tr>
<td>20. Historian, rebuilt 3 houses during last 20 years</td>
<td>solvents, sawdust, silica dust, paint</td>
</tr>
<tr>
<td>21. Builder, wall miller</td>
<td>solvents, sawdust, silica dust, dust</td>
</tr>
<tr>
<td>22. Hospital cleaner</td>
<td>cleaning products</td>
</tr>
<tr>
<td>23. Teacher</td>
<td>no known exposures</td>
</tr>
<tr>
<td>24. Nurse</td>
<td>no known exposures</td>
</tr>
<tr>
<td>25. Unknown (deceased)</td>
<td>unknown (deceased)</td>
</tr>
</tbody>
</table>
Chronic Exposure to Occupational Antigens May Play a Key Role in the Initiation / Maintenance of IgG4-Related Disease

“Blue collar” work
(> 1 year, mostly lifelong)

IAC/AIP (n=25 and 44, resp.)
88 %

PSC (n=21 and 22, resp.)
16 %

Amsterdam

Oxford

61 %
22 %

Maillette de Buy Wenniger, Curver, Beuers. Hepatology 2014: 60:1453

Slide Courtesy U. Beuers, Amsterdam
IgG4 cholangiopathy mimics PSC and CCA

Cholangiographic appearance mimicking primary sclerosing cholangitis (PSC)

Cholangiographic appearance mimicking cholangiocarcinoma (CCA)

Misdiagnosis is common!

Slide Courtesy U. Beuers, Amsterdam

Hubers & Beuers, Viszeralmedizin 2015;31:185
Clinical Features & Diagnosis of PSC

Atypical pANCA
Gut-primed T cells
LPS

HCC

CCA 160x

GB-Ca

Small Duct PSC

~5%

Large Duct PSC

Obliterative fibrosis of bile ducts

PSC-IBD

Modified after G. Paumgartner

Review: Halilbasic et al., Dig Dis 2015

Clinical Features & Diagnosis of PSC

Atypical pANCA
Gut-primed T cells
LPS

HCC

CCA 160x

GB-Ca

Small Duct PSC

~5%

Large Duct PSC

Obliterative fibrosis of bile ducts

PSC-IBD

Modified after G. Paumgartner

Review: Halilbasic et al., Dig Dis 2015
Challenge of Excluding Secondary Causes

- Diagnosis of PSC requires exclusion of secondary causes
  - IgG4-associated cholangitis (IAC)
  - Recurrent bacterial cholangitis
  - Critically ill patients (SC-CIP)
  - Ischemic cholangitis (vs. rPSC)
  - AIDS cholangiopathy
  - Portal hypertensive biliopathy
  - Histiocytosis X, mast cell cholangitis
  - Eosinophilic cholangitis
  - Surgical trauma

Abdalian & Heathcote, Hepatology 2006; 44: 1063
Leonhardt et al., Medicine 2015; 94: e2188
Role of Elevated Serum IgG4 in PSC

Boonstra et al., *Hepatology* 2014; 59: 1954-63
Role of Elevated Serum IgG4 in PSC

• Elevated IgG4 in 10-15% of PSC patients
  – More progressive course; therapeutic implications?¹
• Patients with PSC should be tested at least once for elevated serum IgG4 levels
• Distinction from IAC challenging (overlap?)
• When ↑ serum IgG4 is < 2 x ULN (‘grey zone’), a IgG4/IgG1 ratio >0.24 indicative for IgG4-RD²
• IgG4(+) BCR clones or IgG4/IgG RNA ratio in blood (PCR) can assist differential diagnosis³

1: Mendes et al., *Am J Gastro* 2006; 101: 2070-6
2: Boonstra et al., *Hepatology* 2014; 59: 1954-63
3: Doorenspleet et al., *Hepatology* 2016: 64: 501-7

Novel Approach to Diagnosis & Monitoring of IgG4-related Disease

**Figure 1.** Novel approach to diagnosis and monitoring of IgG4-RD of bile ducts and pancreas. (a): The IgG4/IgG RNA ratio distinguishes IgG4-RD from PSC and hepatobiliary/pancreatic malignancies (cutoff level = 5%, n = 125); (b): AUROC analysis 0.99 (n = 125); (c): Monitoring disease activity by IgG4/IgG RNA during corticosteroid treatment (n = 20).
Autoimmune & Immune-mediated Liver- & Biliary Diseases Can Overlap

IAC = IgG4-associated cholangitis (2007)
often used synonymously for
IgG4-SC = IgG4-related sclerosing cholangitis (2011)
## Comparison of PSC and IgG4-SC

<table>
<thead>
<tr>
<th></th>
<th>PSC</th>
<th>IgG4-SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M:F 1.5:1</td>
<td>M:F 7:1</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Young age (&lt; 40 years)</td>
<td>Older (&gt;50 years)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Cholestatic liver biochemistry</td>
<td>Obstructive jaundice</td>
</tr>
<tr>
<td>Biliary abnormalities</td>
<td>Beading, band-like strictures, peripheral pruning</td>
<td>Long smooth strictures, low CBD stricture</td>
</tr>
<tr>
<td>Raised serum IgG4 levels</td>
<td>&lt;20%</td>
<td>&gt; 70%</td>
</tr>
<tr>
<td>Pancreatic involvement</td>
<td>&lt;5%</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>Multi-organ involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Association with IBD</td>
<td>80%</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>Rare (IgG4 +ve PSC)</td>
<td>Yes (relaps: azathioprine, rituximab?)</td>
</tr>
</tbody>
</table>

- MRI patterns (Tokala et al., *Am J Roentgenol* 2014)
- IDUS (Naitoh et al., *J Gastroenterol Hepatol* 2015)
Comparison of PSC and IgG4-SC

Nakazawa et al., World J Gastroenterol 2013; 19: 7661–7670
Comparison of PSC and IgG4-SC

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>lower CBD stricture</td>
</tr>
<tr>
<td>Type 2</td>
<td>Intrahepatic stenosis with prestenotic dilatation and lower CBD stricture</td>
</tr>
<tr>
<td>Type 3</td>
<td>Hilar stricture and lower CBD stricture</td>
</tr>
<tr>
<td>Type 4</td>
<td>Hilar stricture</td>
</tr>
</tbody>
</table>

*Adapted after Nakazawa et al., WJG 2013*

**Summary of IDUS findings**

- **IgG4-SC**
  - Symmetric
  - clear
  - homogeneous
  - smooth
  - preservation of three layers

- **PSC**
  - Asymmetric
  - heterogeneous
  - unclear
  - irregular
  - disappearance of three layers

*Naitoh et al., J Gastroenterol Hepatol 2015*

---

**References**

Joshi & Webster, *Aliment Pharmacol Ther* 2014; 40: 1251-61

Okazaki et al., *J Hepatol* 2014; 690-95
Cholangiography of PSC versus IgG4-SC

Nakazawa et al., World J Gastroenterol 2013; 19: 7661–7670
Diagnosis of IgG4-related Cholangitis
- HISORt Criteria -

**Biliary strictures:** intrahepatic, proximal and/or distal extrahepatic

A

- Previous pancreatic / biliary resection or core biopsy of pancreas (EUS) showing diagnostic features of AIP / IAC

B

- Classical imaging findings of AIP
- Elevated serum IgG4

C

- Two or more of following:
  - Elevated serum IgG4
  - Suggestive pancreatic imaging
  - Other organ involvement
  - Bile duct / ampullary biopsy with > 10 IgG4-pos. cells/HPF

**Definite IAC**

Improvement after 4 wks of steroid Rx
- Strictures - stent removal
- Liver enzymes < 2 x ULN
- Serum IgG4, CA 19-9

**Probable IAC**

Ghazale et al., *Gastroenterology* 2008;134:706
EASL Clinical Practice Guidelines *J Hepatol* 2009; 51: 237-67
Pitfalls of Elevated Serum IgG4

- sIgG4 normal in >30% of pts. with type I AIP
- Elevated sIgG4 in 5% of healthy individuals
- Elevated sIgG4 in 10% of patients with pancreatic or cholangiocarcinoma (no overlap >4.5 g/L)
- Elevated sIgG4 in various other autoimmune, allergic, inflammatory and infective conditions including PSC
- Elevated sIgG4 does not reliably determine disease activity, disease relapse or organ involvement in AIP (more in systemic disease)
Elevated serum IgG4 is not disease specific

IgG4 level >1.4 g/L

Table 3: Diagnoses of patients with serum immunoglobulin subclass 4 (IgG4) concentrations ≥ 135 mg/dl (n = 210)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cirrhosis with or without HCC</td>
<td>72 (35%)</td>
</tr>
<tr>
<td>Steatosis</td>
<td>35 (17%)</td>
</tr>
<tr>
<td>Viral/toxic hepatitis</td>
<td>24 (11%)</td>
</tr>
<tr>
<td>Cholangitis including IAC</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Pancreatitis including AIP</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Other autoimmune diseases</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Cholecystitis/cholecystolithiasis</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Budd Chiari syndrome</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Other gastrointestinal diseases/malignancies</td>
<td>30 (14%)</td>
</tr>
</tbody>
</table>

Dorn et al., *HPB* 2012
## Diagnostic HISORt Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>- Periductal lymphoplasmacytic infiltrate with obliterative phlebitis</td>
</tr>
<tr>
<td></td>
<td>and storiform fibrosis</td>
</tr>
<tr>
<td></td>
<td>- Lymphoplasmacytic infiltrate with &gt; 10 IgG4+ plasma cells/HPF</td>
</tr>
<tr>
<td><strong>Pancreatic Imaging</strong></td>
<td>Typical: diffuse gland enlargement; diffuse attenuated pancreatic duct.</td>
</tr>
<tr>
<td></td>
<td>Others: focal mass/stricture; atrophy; calcification; pancreatitis</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td>Elevated serum IgG4</td>
</tr>
<tr>
<td><strong>Other organs</strong></td>
<td>Biliary strictures; salivary/lacrimal gland enlarged; mediastinal lymphadenopathy; retroperitoneal fibrosis; lung disease; tubulointerstitial nephritis</td>
</tr>
<tr>
<td><strong>Response to Steroids</strong></td>
<td>Resolution/marked improvement of pancreatic/extrapancreatic manifestation</td>
</tr>
</tbody>
</table>

Treatment of IgG4-related Disease
- International Consensus* (but limited evidence) -

- Multi-system disease
- Frequent pancreatic endocrine and exocrine dysfunction
- Prednisone induction therap similar to AIH
  - Prednisone 30-40mg day and taper by 5mg every 2 weeks
  - Aim at 3-6 mo, some patients require longterm low-dose (5-7.5mg/d)
  - Monitor IgG4 levels (Alk Phos and ALT should also respond)
  - Watch out for hyperglycemia
- Maintenance with Azathioprine, 6-MP or Mycophenolate
- Very bulky pseudo-tumour or early Prednisone relapse
  - Rituximab 1000mg IV q2 weeks for two doses
- Stenting (biliary tract, ureter), rarely surgical debulking

*Khosroshahi et al., Arthritis Rheum 2015; EASL CPG J Hepatol 2009
Ghazale et al., Gastro 2008; Hubers & Beuers, Curr Opin Gastroenterol 2017
Culver & Chapman, Nat Rev Gastro Hepatol 2016
Resolution with steroids
IgG4-associated Cholangitis

Before

After Steroids (3m)

Relapse in 50-60%
Aza, MMF, rituximab

Ghazale et al., Gastroenterology 2008; 134: 706
Mailette de Buy Wenninger et al., Endoscopy 2012; 44. 66
Localization of Strictures in IgG4-associated Cholangitis - Treatment Response to Corticosteroids

Distal Stricture only

Any Proximal strictures

Ghazale et al., Gastroenterology 2008;134:706
Sequential MRCPs of remission and relapse in IAC

At diagnosis (0 months)

18 months

6/12 Pred

Off steroids

30 months

Pred + AZA

28 months

16/12

Slide Courtesy G.J.M. Webster, London
## Treatment of IgG4-related Disease
- Second Line Options (Relapsers, Non-responders)

### Table 4: Immunosuppressive therapies for IgG4-SC*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Regimen</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine‡</td>
<td>2 mg/kg per day in a single dose</td>
<td>Thiopurine analogue, and is the prodrug of mercaptopurine</td>
</tr>
<tr>
<td>Mycophenolate mofetil§</td>
<td>750–1,000 mg twice per day</td>
<td>Inosine-5’-monophosphate dehydrogenase inhibitor</td>
</tr>
<tr>
<td>Mercaptopurine§</td>
<td>2.5 mg/kg per day in two divided doses</td>
<td>Thiopurine analogue</td>
</tr>
<tr>
<td>Methotrexate¶</td>
<td>10–25 mg per week plus folic acid</td>
<td>Antimetabolite and antifolate agent</td>
</tr>
<tr>
<td>Tacrolimus¶</td>
<td>Adjusted to a target blood level range of 4–11 ng/mL</td>
<td>Macrolide calcineurin inhibitor</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1,000 mg week 0 and week 2 by intravenous infusions</td>
<td>CD20⁺ B cell depletion agent</td>
</tr>
</tbody>
</table>

Novel Therapeutic Approaches to PSC
Currently Tested in Clinical Trials

- Gut-

- Primed T cells

- LPS

- Colitis (~75%)

- Microbiota (Dysbiosis)

- FXR

- Antibiotics (Vancomycin, Minocyclin, Metronidazol)

- Cenicriviroc

- Etrolizumab

- Vedolizumab

- norUDCA

- Obliterative fibrosis of bile ducts

- Kowdley et al., AASLD 2017

- AESOP trial (OCA in PSC)
Summary & Conclusions

- IgG4-related disease is a systemic / multiorgan fibroinflammatory condition, pathogenesis still unclear
- Environmental risk factors (“blue collar worker“)
- Diagnosis is based on a combination of clinical, biochemical, radiological and histological findings
- Differentiation from other benign and malignant disorders
- Treatment regimens have been reached by international consensus (no RCT). First-line therapy is corticosteroids, often in combination with (biliary) stenting
- The long-term outcome in IgG4-HBD is not well established. Disease-related inflammatory and fibrotic complications and an increased risk of all-cause malignancy have been reported in prospective studies

Hubers et al., Clin Rev Allergy Immunol 2015; 48: 198-206
Thank you for your attention!
michael.trauner@meduniwien.ac.at