# Addressing challenges in diagnosis and treatment of IgG4-related gastrointestinal disease

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# A conversation between:

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# Agenda

- Challenges of diagnosing IgG4-related gastrointestinal disease
- IgG4-related pancreatitis: Differentiating type 1 autoimmune pancreatitis from type 2
- Therapeutic strategies for IgG4-related gastrointestinal disease

# IgG4-RD is a progressive immune-mediated condition[1–3]

## IgG4-RD was defined as a distinct systemic disease two decades ago[3]

2003

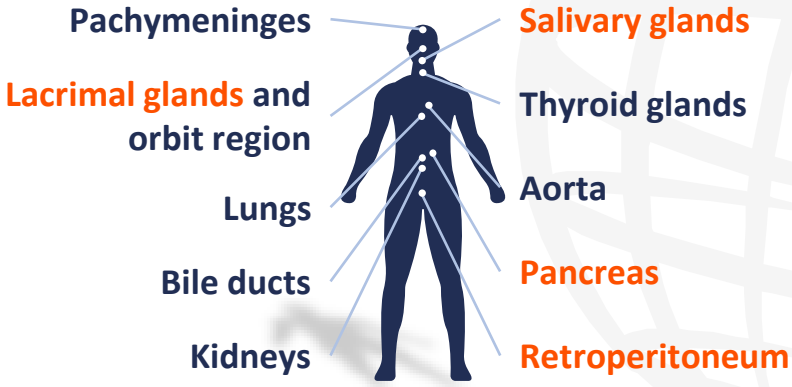
- Relapse–remitting disease course[2]
- Male predominance[2]
- Average age at diagnosis is 50–70 years[2]
- Often presents as a mass lesion or organ enlargement[2]
- Geographic variance in prevalence[4–6]

**Estimated prevalence per 100,000 persons**

0.28–1.08[4,5] 5.3[6]

## >75% of patients with IgG4-RD have two or more organs involved[7]

## Typical organs, involved in IgG4-RD, including those frequently affected[3]




IgG4-RD, immunoglobulin G4-related disease.

1. Tanaka Y, Stone JH. *Mod Rheumatol.* 2023;33:229–36; 2. Katz G, Stone JH. *Annu Rev Med.* 2022;73;545–62; 3. Perugino CA, Stone JH. *Nat Rev Rheumatol.* 2020;16:702–14; 4. Floreani A, et al. *J Transl Autoimmun.* 2021;4:100074; 5. Uchida K, et al. *Int J Rheumatol.* 2012:358371; 6. Wallace ZS, et al. *Ann Rheum Dis.* 2023;82:957–62; 7. Löhr J-M, et al. *Nat Rev Gastroenterol Hepatol.* 2022;19:185–97.

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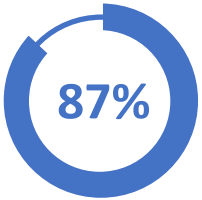
# IgG4-RD often affects the pancreaticobiliary tract[1,2]

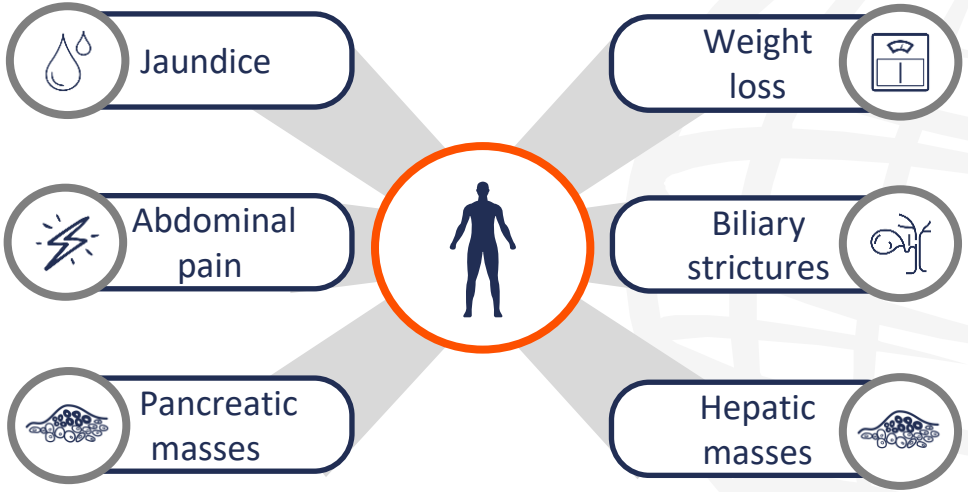
**Pancreatohepatobiliary disease is one of four phenotypes** of IgG4-RD[1]




of patients with IgG4-RD had **pancreatic manifestations** in two large cross-sectional studies[2]

**AIP-1** is the most **common pancreaticobiliary manifestation**[3]

## Clinical presentation of IgG4-related pancreaticobiliary disease[2]




**Cholangitis** is the **most common hepatobiliary manifestation**[2]

AIP-1, autoimmune pancreatitis type 1; IgG4-RD, immunoglobulin G4-related disease.

1. Wallace ZS, et al. *Ann Rheum Dis*. 2019;78:406–12; 2. Löhr J-M, et al. *Nat Rev Gastroenterol Hepatol*. 2022;19:185–97;
3. On W, Huggett MT. *Frontline Gastroenterol*. 2022;13:171–4.

# Features of AIP-1[1]

| | | |
|---|---|---|
| Male:female | 3:1 | |
| Mean age | 65 years | |
| Geography | Asia > Europe and US | |
| Clinical presentation* | Jaundice | 60–80% |
| | Weight loss | 65% |
| | Acute pancreatitis | 15% |
| Biological presentation* | Cholestasis | >80% |
| | Diabetes | 65% |
| | Insulin-dependent diabetes | 20% |
| | Exocrine pancreatic insufficiency | 40% |
| | Lipase | <3 × N |
| IgG4 profile | **>1.35 g/L** (70% sensitivity; 93% specificity)<br>**>2.7 g/L** (53% sensitivity; 99% specificity) | |

Presents as **acute** and **chronic** forms[2]

**Acute presentation:** Obstructive jaundice and/or pancreatic mass[2]

**Chronic presentation:** Pancreatic atrophy, calcifications, ductal dilatation[2]

**Relapse occurs** in 10–20% of patients[2]

*% of cases, where specified.
AIP, autoimmune pancreatitis; Ig, immunoglobulin; N, normal.
1. Mack S, et al. *World J Gastroenterol.* 2022;28:6867–74; 2. Löhr J-M, et al. *Nat Rev Gastroenterol Hepatol.* 2022;19:185–97.

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# AIP-1 and AIP-2 are distinct diseases

| | AIP-1 (IgG4-related pancreatitis)[1] | AIP-2 (IDCP or AIP with GELs)[1] |
|---|---|---|
| Male:female | 3:1 | 1:1 |
| Mean age | 65 years | 40 years |
| Geography | Asia > Europe and US | Europe and US > Asia |
| Clinical presentation* | Jaundice 60–80%<br>Weight loss 65%<br>Acute pancreatitis 15% | Acute pancreatitis 80%<br>Jaundice 30% |
| Biological presentation* | Cholestasis >80%<br>Diabetes 65%<br>Insulin-dependent diabetes 20%<br>Exocrine pancreatic insufficiency 40%<br>Lipase <3 × N | Endocrine and exocrine pancreatic insufficiency Rare<br>Lipase >3 × N |
| IgG4 profile | **>1.35 g/L** (70% sensitivity; 93% specificity)<br>**>2.7 g/L** (53% sensitivity; 99% specificity) | Not elevated[2] |

**AIP-2 has no relationship to IgG4-RD[3]**

*% of cases. AIP, autoimmune pancreatitis; GEL granulocyte epithelial lesion; IDCP, idiopathic duct-centric pancreatitis; IgG4-RD, immunoglobulin G4-related disease; N, normal.

1. Mack S, et al. *World J Gastroenterol.* 2022;28:6867–74; 2. Wang H, et al. *BMC Gastroenterol*. 2021;21:421; 3. Blaho M, et al. *Adv Med Sci*. 2020;65:403–8.

# Treatment of pancreaticobiliary manifestations of IgG4-RD

## Induce remission[1,2]

**GCs**
e.g. prednisolone
40 mg/day for 4 weeks

**Dose tapering after 1 month if response is achieved;**
taper at a rate of
5 mg every 1–2 weeks

## Maintain remission[1,3]

**Low-dose GCs**
e.g. prednisolone
2.5–10 mg/day

**Steroid-sparing agents**, **immunosuppressants** and **B-cell depletion** (off-label)

## Monitor for treatment response and relapse[1,3–5]

**Sequential clinical, biochemical and radiological evaluation**

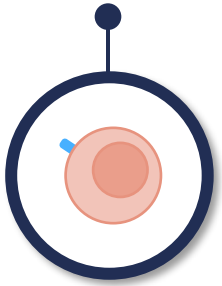
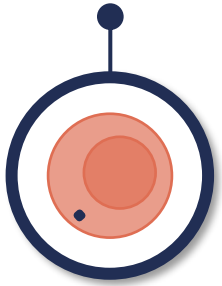
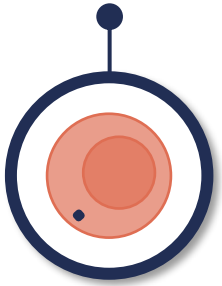
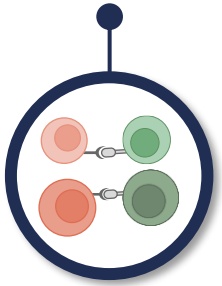
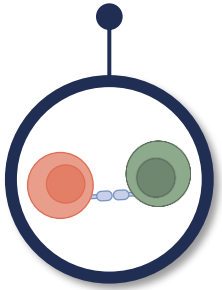
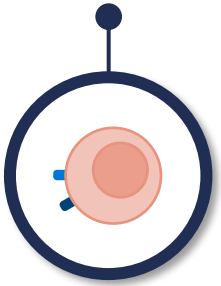
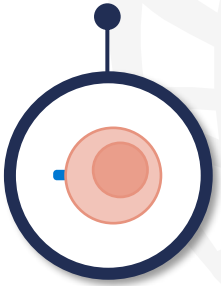
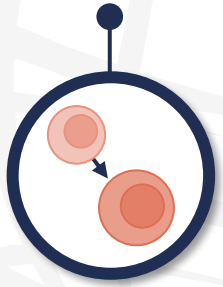
**Relapses treated with GCs**
(re-induction and prolonged tapering) or **adjunct immunosuppressants** or **B-cell depletion** (off-label)

**Treatment goals in IgG4-RD are to alleviate symptoms, prevent progression and mitigate relapse risk[1,4,6–9]**

GC, glucocorticoid; GI, gastrointestinal; IgG4-RD, immunoglobulin G4-related disease.

1. On W, Huggett MT. *Frontline Gastroenterol.* 2022;13:171–4; 2. Perugino CA, Stone J. *Z Rheumatol.* 2016;75:681–6; 3. Majumder S, et al. *Clin Gastroenterol Hepatol.* 2018;16:1947–53; 4. Kuraishi Y, et al. *Pancreatology.* 2020;20:1062–8; 5. Hart PA, et al. *Gut.* 2013;62:1607–15; 6. Maruyuma M, et al. *Int J Rheumatol.* 2013;272595; 7. Löhr J-M, et al. *United European Gastroenterol J.* 2020;8:637–66; 8. Löhr J-M, et al. *Nat Rev Gastroenterol Hepatol.* 2022;19:185–97; 9. Okazaki K, et al. *Mod Rheumatol.* 2023;33:237–41.

# Novel targeted agents are in clinical development[1–4]

| Phase I/II | Phase II | | | | Phase III | | Phase IV |
|---|---|---|---|---|---|---|---|
| **Rituximab** | **Rilzabrutinib** | **Zanubrutinib** | **Abatacept** | **Elotuzumab** | **Obexelimab** | **Inebilizumab** | **Belimumab** |
| NCT01584388 **Completed** | NCT04520451 **Active** | NCT04602598 **Recruiting** | NCT03669861 **Completed** | NCT04918147 **Recruiting** | NCT05662241 **Recruiting** | NCT04540497 **Active** | NCT04660565 **Unknown** |
|  |  |  |  |  |  |  |  |
| Anti-CD20 antibody | BTK inhibitor | BTK inhibitor | CTLA4-Ig fusion protein | Anti-SLAMF7 antibody | Anti-CD19 antibody | Anti-CD19 antibody | Anti-BAFF antibody |

BAFF, B-cell activating factor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; CTLA4, cytotoxic T-lymphocyte associated protein 4; Ig, immunoglobulin; SLAMF7, surface antigen CD319.

1. Nakayamada S, Tanaka Y. *Mod Rheumatol*. 2023;33:266–70; 2. Lanzillotta M, et al. *Mod Rheumatol*. 2023;33:258–65; 3. Tanaka Y, Stone JH. *Mod Rheumatol.* 2023;33:229–36; 4. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ searchable by NCT number (accessed November 2023).