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## Autoimmune pancreatitis type 1 and type 2: what we know so far

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## **Abstract**

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis characterized by lymphoplasmacytic infiltration, pancreatic fibrosis, and responsiveness to steroid therapy. It is classified into two histological subtypes: Type 1 (Lymphoplasmacytic Sclerosing Pancreatitis, LPSP) and Type 2 (Idiopathic Duct-centric Pancreatitis, IDCP). Type 1 AIP, associated with IgG4-related disease, typically affects older males and often involves other organs, whereas

Type 2 AIP, more common in younger patients and linked to inflammatory bowel diseases, is limited to the pancreas. Diagnosis, which differentiates AIP from pancreatic cancer, relies on histopathology, imaging, serology, organ involvement, and steroid responsiveness, guided by the Mayo Clinic HISORt and International Consensus Diagnostic Criteria (ICDC).

The pathogenesis of AIP involves complex immunological, genetic, and environmental factors, with Type 1 characterized by IgG4-producing plasma cells and Type 2 by granulocytic infiltration. Treatment predominantly involves corticosteroids, effective for both types but with a higher relapse rate in Type 2, necessitating long-term immunosuppressive therapies such as azathioprine, mycophenolate mofetil, and rituximab. Emerging biological therapies targeting specific immune pathways show promise.

This review highlights the clinical presentation, diagnostic challenges, pathophysiology, and therapeutic approaches for AIP, emphasizing the need for ongoing research to improve diagnostic accuracy and develop more effective, targeted treatments.

Keywords: AIP, gastroenterology, autoimmune diseases, pancreatitis, biological treatment

## **Introduction**

### Definition

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis characterized by obstructive icterus, lymphoplasmacytic infiltrate with pancreatic parenchyma fibrosis and a positive response to steroid treatment<sup>1</sup>. Based on the histological subtype AIP is classified as type 1, also called lymphoplasmacytic sclerosing pancreatitis (LPSP), and type 2, also called idiopathic ductal centric pancreatitis (IDCP)<sup>2</sup>. The pathogenesis of AIP still remains unclear. Autoimmune pancreatitis types vary in epidemiology, symptoms, and histologic pattern.

LPSP is considered to be pancreatic manifestation of IgG4-related disease (IgG4-RD) and also involves other organs AIP 1 can be manifested by retroperitoneal fibrosis, chronic periaortitis, autoimmune hypophysitis, sclerosing cholangitis, Riedel's thyroiditis, and Mikulicz disease<sup>3</sup>. Contrary, AIP 2 is not a systematic disease, its localization is limited to pancreas. AIP 1 is characterized by elevated IgG4 serum level, while the elevation of IgG4 levels in AIP 2 is not reported<sup>4</sup>. Type 2 AIP typically shows duct-centric pancreatitis with granulocytic epithelial

lesions, which can eventually obliterate the pancreatic duct<sup>5</sup>. In approximately 30% of cases, AIP 2 is associated with inflammatory bowel disease (IBD), especially ulcerative colitis (UC). The connection with IBD in AIP 1 is rare<sup>6</sup>. It was observed that relapse rates of AIP-1 are lower compared to AIP-2. Autoimmune pancreatitis types vary in diagnostic processes. Pancreatic biopsy has to be performed only in AIP 2 diagnosis. Although, these conditions differ in many aspects, both respond well to steroid therapy<sup>2</sup>. The characteristic of main differences between AIP-1 and AIP-2 is presented in *Table 1*.

	Type 1 autoimmune pancreatitis	Type 2 autoimmune pancreatitis
Prevalence	<i>Asia &gt; USA/Europe</i>	<i>USA/Europe &gt; Asia</i>
Age of onset	<i>&gt;50 years old</i>	<i>30-50 years old</i>
Gender	<i>Male &gt; Female</i>	<i>Male = Female</i>
Worldwide percentage	<i>&gt;90</i>	<i>&lt;10</i>
IgG4 serum level	<i>elevated</i>	<i>normal</i>
Other organs manifestation	<i>yes</i>	<i>no</i>
Association with IBD	<i>rare</i>	<i>common</i>

*Table 1. Characteristic of main differences between AIP-1 and AIP-2.*

### Epidemiology

The exact prevalence and incidence of AIP is unknown. The epidemiological data of AIP are not clear due to the worldwide differences of diagnostic criteria. Since the international consensus has been made, the same diagnostic criteria are used worldwide. It was reported that AIP incidence in Germany is less than 1 per 100,000 inhabitants (7). A representative study from Japan, shows a prevalence of 4.6 per 100,000 inhabitants and an incidence of 1.4 per 100,000 inhabitants<sup>8</sup>. It was also indicated that AIP 1 was detected much more frequently than AIP 2. The median age of patients at diagnosis was 48 and 62,5 for AIP 1 and AIP 2, respectively<sup>9</sup>. It was observed that males suffer from AIP 1 more often than females, while in AIP 2 there was no significant difference in terms of gender. Moreover, there are more AIP 1 cases in Asia than in Europe<sup>10</sup>.

### Clinical presentation

AIP 1 and AIP 2 are characterized by different clinical presentation. One of the most common symptom of AIP 1 is painless jaundice, resulting from compression of the common bile duct by the enlarged pancreas. AIP 1 is also often connected with abdominal pain and weight loss. Exocrine pancreatic insufficiency manifests as fatty stools and bloating. Moreover, in AIP 1 can occur lymphadenopathy and symptoms from other organs such as sclerosing cholangitis, interstitial nephritis and pneumonitis. In AIP 2 abdominal pain is more prominent and often recurrent. Contrary to AIP 1, in type 2 jaundice is less common and other organs are rarely involved. Similar to AIP 1, AIP 2 is connected with exocrine pancreatic insufficiency presenting with steatorrhea.

### Diagnosis

The diagnosis of AIP may be challenging for the clinicians. The symptoms can be various and mainly manifested as acute pancreatitis, upper abdominal pain, or obstructive painless jaundice. AIP can be asymptomatic as well or give general symptoms such as weakness, and weight loss. Prior to introducing treatment, it is crucial to rule out pancreatic cancer whose symptoms can mimic AIP. There are a few key features that can be valuable in identifying AIP known as Mayo Clinic HISORt criteria: histopathology, imaging of pancreatic parenchyma and duct, serology, organ involvement, and response to the corticosteroid therapy. International Consensus Diagnostic Criteria for AIP (ICDC) was reached by revision of already existing criteria by a panel of experts.

### Pathophysiology

The pathogenesis of AIP is still not fully understood, but it is supposed to be multifactorial involving an interplay of immunological, genetic, and environmental factors<sup>11</sup>. The origin of AIP is considered to involve autoimmune processes that lead to the infiltration of immune cells into pancreatic tissue, in particular CD 4+ T cells, granulocytes in AIP 2 and IgG4- producing plasma cells and B-lymphocyte antigen CD20 in AIP 1<sup>12</sup>. It was shown that plasmacytoid dendritic cells (pDCs) may also have an influence on AIP pathogenesis<sup>13</sup>. However, the exact mechanism remains unknown and some of the research on the mechanism of AIP should be continued with the hope of finding new, more effective methods of treatment.

## **Treatment**

### Steroids

Both types of AIP are usually responsive to corticosteroid treatment. The relapse rate is significantly higher in AIP 1, compared to AIP 2<sup>14</sup>. In Europe, recommended minimal dose of

prednisone is 20 mg/day, typically 30-40 mg per day. The therapy should be continued for the next 4 weeks and then the dosage is tempered to 5-7,5 mg/day as a maintenance treatment (MLDST)<sup>1516</sup>. MLDST contributes to the reduction of many adverse effects related to the main disease such as recurrent obstructive jaundice. MLDST should last for approximately 12 weeks<sup>17</sup>, although other guidelines suggest a duration of up to 6 months or even 3 years<sup>14</sup>, the latter if the relapse risk is high. In unresponsive patients, steroid mini pulse can be considered. Sugimoto et al. suggests the administration of two courses of methylprednisolone at a dosage of 500 mg/day for the next 3 days with a 4-day interval<sup>18</sup>. There were no substantial disparities observed in the 5-year cumulative relapse-free survival rate between the oral and pulse groups<sup>18</sup>. In asymptomatic patients, the usage of corticosteroids should be considered as well<sup>19</sup>. It is necessary to monitor and note the side effects of the steroid therapy. The most common are: diabetes, ulcers, glucose intolerance, osteoporosis, dyslipidemia and hypertension. If the corticosteroid treatment leads to numerous side effects, the implementation of biological therapies should be considered, e.g., rituximab.

#### Immunomodulatory therapy

Azathioprine (AZA) is an analog of purines that is transferred to active metabolites such as mercaptopurine (6MP) and thioguanine (TGN). AZA mode of action is based on disruption of DNA replication in lymphocytes which do not possess any alternative pathway of purine synthesis and stimulating alloreactive T lymphocytes response<sup>20</sup>. De Pretis et al. evaluated the efficiency and safety of AZA in the maintenance therapy of AIP, especially in relapsing AIP<sup>121</sup>. However, a mice study performed by Schwaiger et al. shows that the use of AZA for inducing remission did not demonstrate a beneficial impact on AIP, unlike cyclosporine A and rapamycin<sup>22</sup>.

Cyclosporine A (CA) is an inhibitor of calcineurin, which was tested on 19 cats with chronic pancreatitis by Hoeyrup et al. The results confirm CA's favorable effect when it comes to inducing remission<sup>23</sup>. Further studies are necessary to assess the influence of CA on AIP. Mycophenolate mofetil (MM) can also be considered as an alternative option for treatment. MM acts as a prodrug that prevents lymphocytes T and B from proliferation. MM's mechanism of action limits inosine monophosphate dehydrogenase (IMPDH) causing depletion of guanosine in nucleotides. Sodikoff et al. reported a case of a 65-year-old male with AIP where prednisone and MM were administered. Previously he was administered azathioprine, but with poor tolerance. In the end, despite the improvement of the patient's clinical condition, it was not feasible to decrease the daily dose of prednisone despite the administration of MM. MM was discontinued, and the patient returned to a prednisone dose of 15mg per day, while efforts

were made to explore alternative medications that could potentially alleviate the symptoms of AIP<sup>24</sup>.

### Rituximab

Rituximab (RTX) is a monoclonal chimaeric antibody that binds specifically to surface protein CD20 expressed on the B-lymphocytes<sup>25</sup>. It leads to the depletion of B-cells in the peripheral blood and contributes to reduction of the autoimmunological response. RTX is approved for the treatment of AIP-1 patients who are resistant to or cannot tolerate high-dose GC. It has been also found as an alternative agent if immunomodulatory therapies have failed. RTX, contrasted with IM, performs more specific interference into the plasmablast -initiated AIP—1 pathology<sup>26</sup>. The research conducted by Soliman et al. has shown that RTX treatment was more effective than IM drugs. The efficacy of treatment with immunomodulatory drugs reached 65%, while RTX had 94,1% of effectiveness. It has been also reported that RTX influenced the normalization of IgG4 serum level and decrease in elevated liver enzymes<sup>27</sup>. Another study conducted in 12 patients resistant IM reports, that 83,3% of them were treated successfully with rituximab. No RTX adverse events were observed<sup>28</sup>. It has been also proven that RTX induced remission in the group of patients suffering from different manifestations of IgG4-RD, including nephritis<sup>29</sup>. The retrospective analysis of results of RTX treatment in large cohort of AIP patients has been performed by Nikolic et al. Twelve patients received RTX, and complete remission was achieved in 66.7%. During a median follow-up of 17 months, none of them relapsed<sup>30</sup>. The results mentioned above confirm that RTX induces remission and prevents relapse in AIP-1. Therefore, in some cases, RTX can be also recommended as maintenance therapy. The comparison between induction and maintenance therapy and induction therapy alone was made. The results showed that only 11% of patients with continuation of RTX treatment after induction relapsed, compared with 45% patients with only induction therapy<sup>31</sup>. It was indicated that relapse after RTX treatment is more likely to appear in group of younger patients with biliary disease and higher IgG4 responder index score.

Treatment options including GCs and IM drugs influence protective immunity and often cause serious adverse events. Rituximab, safety profile and its efficacy far outweigh the possible risk of side effects. RTX side effects study showed, that one of the patients had to end RTX therapy after 16 months, because skin manifestation of *Borrelia* reactivation occurred. The reactivation of tuberculosis after the first induction dose also appeared in another patient causing the termination of the therapy<sup>30</sup>. In the observational cohort study, 989 patients with rheumatoid arthritis (RA) received RTX according to their physician's standard practice and were evaluated at standard-of-care follow-up visits at least every 6 months<sup>32</sup>. The study reports that 19,9%

patients developed serious infections such as pneumonia, cellulitis, urinary tract infection, bronchitis, and sepsis. The connection between cumulative rituximab exposure and the incidence of serious infections was not observed. The opportunistic infections were observed less often (1.9%). During RTX therapy some patients, who suffered from RA, presented cardiovascular and thrombotic events: myocardial infarction (1.8%), deep vein thrombosis (1,2%) and pulmonary embolism (1,0%).

As it is presented, rituximab therapy is effective in inducing and maintaining the remission of AIP-1. The rate of side effects connected with use of RTX is low. RTX is suggested to be efficient and safe alternative in patients who were not treated successfully with GCs or immunomodulatory drugs.

#### Other Biological Therapies

There are few reported cases of AIP patients treated with anti-tumor necrosis factor antibodies (anti-TNF). Lorenzo et al. described the first case of steroid dependent AIP type 2, that was effectively managed by anti-TNF<sup>33</sup>. Adalimumab (anti-TNF antibody) was administered to 28-year-old woman, with a histologically confirmed diagnosis of AIP 2 without accompanying IBD. Previously, the patient did not respond to steroids and RTX therapy. Adalimumab was administered in three doses without maintenance therapy. After an 11-month follow-up period, there was not AIP recurrence. The effectiveness of adalimumab in AIP was also shown in case of young patient with IgG4 positive colitis<sup>34</sup>. The colitis was resistant to GCs and IM therapies, but sustained response was reported after introduction of 160/80 mg dose of adalimumab followed by 40 mg weekly. After three months, there was no IgG4 positive colonic infiltrate showed in sigmoidoscopy. These cases demonstrate that knowledge about anti-TNF agents can exert a positive impact on AIP emergency treatment development.

The expression of type 1 interferons (INF-1) and interleukin-33 (IL-33) is enhanced in AIP and promotes inflammation and fibrosis. Interestingly, it was also suggested that plasmacytoid dendritic cells (pDCs) can be a vital target for AIP treatment. The reduction of pDCs results in inhibition of the production of INF-1 and IL-33 and leads to alleviation of experimental AIP<sup>35</sup>. As IL-33 pathway is implicated in the pathogenesis of AIP, it can be also relevant to use etokimab as additional drug. The therapeutic implications of etokimab were presented in atopic dermatitis and its promising potential in autoimmune diseases was suggested<sup>36</sup>.

Inebilizumab is a humanised anti-CD19 monoclonal antibody that reversibly inhibits B cells. In 2020, it was approved as a treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients. Currently, inebilizumab undergoes clinical trials for kidney transplant desensitization, myasthenia gravis, and IgG4-related disease<sup>37</sup>.

Moreover, in pancreatic tissues of patients affected by AIP type 1, M2-polarized macrophages were described. In comparison to pro-inflammatory properties of M1 macrophages, M2 macrophages are polarized by Th2 cytokines and produce anti-inflammatory cytokines<sup>38</sup>. It was also proven that M2 macrophages contribute to tissue repair by influencing angiogenesis. The therapeutic influence of M2 macrophages should be considered in AIP 1 management<sup>39</sup>.

## **Conclusions**

Autoimmune pancreatitis is a unique and complex form of chronic pancreatitis that presents distinct diagnostic and therapeutic challenges. Characterized by lymphoplasmacytic infiltrate, fibrosis of the pancreatic parenchyma, and a positive response to steroid treatment, AIP is divided into two histological subtypes: AIP 1 and AIP 2.

AIP 1 is predominantly seen in older males and is more prevalent in Asia. It is associated with elevated serum IgG4 levels and systemic involvement of other organs, manifesting as part of IgG4-related disease. Common clinical presentations include painless jaundice, weight loss, and exocrine pancreatic insufficiency. The disease responds well to corticosteroid treatment, although the relapse rate remains a concern.

AIP 2, more common in Europe and the USA, typically affects a younger demographic with no gender predilection. It is not associated with elevated IgG4 levels and is confined to the pancreas. Unlike Type 1, Type 2 AIP is often linked to inflammatory bowel diseases, especially ulcerative colitis. The clinical presentation includes more pronounced abdominal pain and recurrent episodes. The relapse rate in Type 2 AIP is higher, necessitating meticulous long-term management.

The pathogenesis of AIP remains incompletely understood, but it is believed to involve complex interactions between immunological, genetic, and environmental factors. Type 1 AIP is characterized by immune cell infiltration, particularly IgG4-producing plasma cells, while Type 2 AIP shows granulocytic infiltration and duct-centric lesions.

Diagnosing AIP requires careful differentiation from pancreatic cancer due to overlapping symptoms. Key diagnostic criteria include histopathology, imaging, serology, organ involvement, and response to corticosteroid therapy, with the Mayo Clinic HISORT criteria and the International Consensus Diagnostic Criteria (ICDC) being widely used.

Treatment primarily involves corticosteroids, which are effective in inducing remission for both types. However, due to the higher relapse rates, particularly in Type 2, additional immunosuppressive agents such as azathioprine, mycophenolate mofetil, and rituximab may be

employed. Emerging therapies, including biologics like anti-TNF agents and those targeting specific immune pathways, show promise for future management.

In conclusion, AIP is a rare yet significant disease requiring a nuanced understanding of its distinctive features for accurate diagnosis and effective treatment. Ongoing research into its pathogenesis and therapeutic approaches is crucial for improving patient outcomes and developing more targeted treatment strategies.

#### **Author's contribution**

Conceptualization, Marta Piotrowska; methodology, Julita Gmitrzuk and Martyna Opatowska; software, Tomasz Kucharski and Joanna Jakubiec; check, Katarzyna Wiśniewska and Marta Piotrowska; formal analysis, Julita Gmitrzuk and Zuzanna Malinka; investigation, Julita Gmitrzuk and Anna Jachymek; resources, Martyna Opatowska and Tomasz Kucharski; data curation, Joanna Jakubiec, Katarzyna Wiśniewska; writing – rough preparation, Julita Gmitrzuk; writing - review and editing, Julita Gmitrzuk and Marta Piotrowska; visualization, Julita Gmitrzuk, Zuzanna Malinka and Anna Jachymek; supervision, Daria Aleksandrowicz and Martyna Opatowska; project administration, Julita Gmitrzuk, Daria Aleksandrowicz. All authors have read and agreed with the published version of the manuscript.

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