Treatment approaches in autoimmune pancreatitis (Review)

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Abstract. Autoimmune pancreatitis (AIP) is a rare disease. There are two distinct types of AIP: AIP type 1 (AIP-1), a pancreatic manifestation of a multi-organ disease linked to immunoglobulin (Ig)G4, and AIP type 2 (AIP-2), a pancreas-specific disease unrelated to IgG4. The usual course of treatment for AIP is oral corticosteroid medication. Rituximab has also been recommended for recurrent AIP-1 in order to initiate remission and provide ongoing treatment. Immunomodulators such as azathioprine are used to keep certain patients in remission. Evaluation also takes into account a number of pharmacological alternatives, including biologic drugs like anti-tumor necrosis factor therapy, a safe and efficient second-line treatment for AIP-2 relapse or steroid dependence. Corticosteroids and immunosuppressants, which are poorly tolerated due to considerable side effects, are being replaced by other biologic drugs, which may offer a beneficial therapeutic alternative.

Contents

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1. Introduction

A type of pancreatitis known as autoimmune pancreatitis (AIP) is brought on by aberrant autoimmune processes. According to the International Consensus Diagnostic Criteria 2010 (ICDC) (1), AIP is a distinct type of pancreatitis characterized by obstructive jaundice, lymphoplasmacytic infiltration and fibrosis, and a notable response to steroids (1).

Recently, there has been a marked increase in the incidence of acute pancreatitis of unspecified aetiology, suggesting the possibility that SARS-CoV-2 may be an etiological factor in the development of this condition (2-4). This perspective raises the need for further research to investigate potential links between SARS-CoV-2 infection and AIP, thus contributing to a better understanding of this complex condition.

The prevalence of AIP is relatively low. In a study of 178 patients with suspected pancreatitis, only seven patients (3.9%) were diagnosed with this condition. From a study of 63 patients with AIP, 22 patients (34.9%) presented features of acute or chronic pancreatitis at diagnosis, highlighting the diagnostic challenges and the need for a careful approach (5).

AIP type 1 (AIP-1), an immunoglobulin (Ig)G4-related disease (IgG4-RD), and AIP type 2 (AIP-2) are the two subtypes of AIP (1,6,7). Clinically, obstructive jaundice with or without a pancreatic mass is a common symptom of AIP, which is also defined histologically by a lympho-plasmacytic infiltration and fibrosis, and therapeutically by a notable reaction to steroids (1,8). It was first described by Sarles *et al* (9) in 1961 as chronic inflammatory sclerosis of the pancreas, and Yoshida *et al* (10) named it AIP in 1995 after noticing clinicopathological parallels to autoimmune hepatitis.

$IgG4^+$ plasma cell infiltration, lymphoplasmacytic sclerosing pancreatitis, pancreatic edema, pancreatic duct constriction and obliterative phlebitis are the characteristics of AIP-1 (11,12). By contrast, AIP-2 is defined by granulocytic

epithelial lesions which histopathologically suggest idiopathic duct-centric chronic pancreatitis (11,12). AIP-2 starts earlier than AIP-1, and is frequently aggravated by inflammatory bowel disease (IBD), especially ulcerative colitis (UC) (13).

According to available data, AIP-1 appears to be the most predominant form of AIP. A national Japanese study revealed that the annual number of patients with AIP-1 is 0.71 per 100,000 individuals, representing 2% of patients with chronic pancreatitis (14).

AIP-2 is predominant in western countries and is characterized by an equal incidence between men and women, without a specific sex deviation (15). It has also been noted that 16-30% of cases of AIP-2 are associated with IBD, such as UC (16,17).

Regarding AIP risk factors, there are notable differences between the two main types. For AIP-1, a long-term Japanese study involving 624 patients identified the formation of pancreatic stones as a notable risk factor, associated with lower values of the bentiromide test at diagnosis and higher values of haemoglobin A1c after treatment with corticosteroids, as well as a higher frequency of pancreatic atrophy and stenosis of the hilar or intrahepatic bile duct in patients with pancreatic stone formation (18). On the other hand, in the case of AIP-2, risk factors for recurrence include initial use of steroids and tobacco, and the presence of chronic pancreatitis as highlighted in a study that included 162 patients with AIP-1 and -2 with an average follow-up of 3 years (19).

The diagnosis of AIP is markedly different between the two main types of the disease. In the case of AIP-1, diagnosis is based on a combination of clinical, imaging and serological criteria, including increased levels of serum IgG4 and distinctive radiological features, such as diffuse or focal thickening of the pancreas and the presence of a peripancreatic 'halo' in magnetic resonance imaging or computed tomography (20). On the other hand, the diagnosis of AIP-2 requires a multidisciplinary approach, including histological evaluation through endoscopically guided biopsy, the presence of associated IBD and a positive response to steroid therapy in the absence of specific serological markers such as IgG4 (21).

The epidemiology, histological pattern, pathogenesis and natural history of AIP-1 and -2 are distinct from one another. Patients with AIP who cannot be categorically categorized as either AIP-1 or -2 are referred to as having AIP-not otherwise specified (AIP-NOS) (1). It can be overlap syndrome, unidentified AIP-2 or IgG4-seronegative AIP-1. Ikeura *et al* (22) estimated that 16% of AIP diagnoses are caused by AIP-NOS.

2. Materials and methods

Using the search terms 'autoimmune pancreatitis', 'International Consensus Diagnostic Criteria', 'glucocorticoids', 'azathioprine' and 'rituximab', studies were examined using the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/home.uri) and EMBASE (https://www.embase.com/landing?status=grey) databases. Only the most pertinent articles were included in the present review after authors individually assessed publications in English for relevancy. Letters, comments and opinions were excluded from the search.

3. Treatment

International guidelines have been put together by experts from a number of nations for the management of AIP globally (1). One of the diagnostic criteria for the diagnosis of AIP is a steroid trial (0.6-1 mg/kg prednisone) with review of imaging and carbohydrate antigen 199 levels after 2 weeks of treatment. In patients with AIP, a clear improvement in imaging abnormalities such as biliary structures and pancreatic enlargement is anticipated (1).

According to previous research, 10-25% of patients with IgG4-RD exhibit spontaneous symptom remission without medical intervention (23), while the relevant percentage reported by Hart *et al* (24) was ≤55. All symptomatic patients should be treated, sometimes promptly in cases of organ failure brought on by notable inflammatory processes such as obstructive jaundice, abdominal pain, posterior pancreatic discomfort and other organ involvement.

In order to reduce the danger of exocrine or endocrine insufficiencies, people with AIP without symptoms should not be treated, according to the available data (1). Steroids are the first-line treatment for all patients with active AIP, according to the international consensus for the condition (1).

Rituximab (RTX) is the only steroid-sparing therapy with proven efficacy in leading to remission as a single agent in cases of contraindication to steroids, while other steroid-sparing medicines such as thiopurines are ineffective when administered as monotherapy (23).

Clinical complete remission is defined as the absence of symptoms, return to normal blood IgG/IgG4 levels, and absence of the usual pancreatic hypertrophy and irregular pancreatic duct narrowing. One or two of these conditions must be satisfied for there to be an incomplete remission. After beginning steroid medication, symptoms and radiographic remission can be seen 2-4 weeks later (25).

After complete or partial remission of AIP, relapse is defined as the return of clinical, serological, radiological or histological abnormalities (23). After remission, some patients with AIP-1 might need to continue receiving low-dose glucocorticoids (GCs), immunosuppressive medication or RTX (23). Determining disease activity based on imaging results, serum IgG4 levels and the presence or absence of extrapancreatic lesions is crucial for deciding if maintenance medication is required (25,26).

Low dose steroids (2.5-7.5 mg/day), immunomodulators or RTX are recommended drugs for maintenance therapy. Japanese doctors advise the use of low-dose GC maintenance therapy for ≤3 years, while the duration of maintenance therapy is still debatable. Maintenance therapy should be scheduled to terminate in instances of radiographic and serological improvement (27).

Steroids. The expression of numerous proinflammatory cytokines such as IL4, IL10 and IL13, a number of which are involved in the pathophysiology of AIP, is inhibited by GCs (25). The initial dose range of prednisone should be 0.6-0.8 mg/kg per day (usually 30-40 mg/day prednisone equivalent), for 1 month, with the effectiveness of the treatment being assessed after 2-4 weeks according to United European Gastroenterology and the Swedish Society of Gastroenterology evidence-based

recommendations (6). Prednisone dosage needs to be reduced by 5 mg every 2 weeks after that, and it should be stopped after 3-6 months (6). A steroid mini-pulse treatment (two courses of methyl-prednisolone 500 mg x 3 days with 4 days intervals) may be useful in cases of individuals who are refractory (23). AIP relapse after or during first treatment is frequent and poses a difficult dilemma in clinical practice, despite the ease with which remission is achieved in the majority of instances of AIP following corticosteroid induction therapy. A total of ≤33% of patients who receive effective steroid induction therapy may experience disease recurrence. In that situation, extending low-dose steroid therapy beyond 1 year could lower the likelihood of relapse (23).

Relapses occur more frequently in patients with AIP-1 than in patients with AIP-2 (37.5 vs. 15.9%, respectively). The most notable risk factors for AIP relapse are deemed to be high IgG4 levels, jaundice and involvement of retroperitoneal fibrosis, chronic periaortitis, autoimmune hypophysitis, sclerosing cholangitis and Riedel's thyroiditis (28,29).

Since western researchers opposed the routine use of maintained GC in cases of AIP with initial remission, Japanese guidelines instead (27,28) recommend the administration of a GC maintenance therapy for 3 years in all patients with AIP-1 to reduce the risk of relapse. At present, the approaches to maintenance steroid therapy vary significantly across the globe.

Yoon *et al* (30) recently reported that patients with AIP-1 experience a lower relapse rate after receiving GC treatment for ≤36 months. However, the negative effects of long-term GC therapy raise concerns regarding this treatment approach.

Steroid-sparing agents. Conventional GC-sparing drugs, such as azathioprine (AZA), 6-mercaptopurine, mycophenolate mofetil (MMF), cyclosporine A, tacrolimus, methotrexate and cyclophosphamide, may be taken into consideration to prevent long-term side effects of GC therapy (6). Although there are few studies (5,6) supporting the use of one drug over another, AZA (2-2.5 mg/kg body weight) is typically recommended. According to a previous meta-analysis, MMF was the second most prescribed medication, while AZA was administered in 85% of cases of relapse (31). De Pretis *et al* (32) validated the effectiveness and safety of AZA in a retrospective investigation of its use in AIP, and also demonstrated that patients with AIP-1 were treated more frequently. Masaki *et al* (33) conducted a systematic review and meta-analysis to examine the efficacy of AZA, despite the lack of clinical trials on its use in AIP. They found no AZA-treated patients who were naive to corticosteroid treatment, but they hypothesized that AZA might be effective as a maintenance therapy in patients with AIP who repeatedly relapse or are steroid-resistant. A few restrictions were applied to the meta-analysis: It was not possible to adequately categorize patients with AIP (AIP-1 vs. AIP-2) because all data were from western nations and involved different doses (50 mg/day or 100 mg/day) (33). That study also looked at the negative effects associated with treatment with AZA; the most frequent ones were pancreatitis, gastrointestinal issues, liver damage, severe leukopenia and hair loss. Although there is a small chance of developing acute pancreatitis after receiving AZA, it is uncertain how frequently AZA-induced pancreatitis affects patients with AIP (32,34).

In a previous retrospective cohort study, Wilson *et al* (35) discovered that the HLA-DQA1-HLA-DRB1 polymorphism is an important marker of the risk of developing AZA-induced pancreatitis; when evaluating the HLA-DQA1*02:01-HLA-DRB1*07:01 polymorphisms, three groups were distinguished: i) Extensive metabolizers with wild-type genotype; ii) intermediate metabolizers with heterozygous variation genotype; and iii) poor metabolizers with homozygous variant genotype, who should thus receive alternative treatment (35).

RTX. According to European recommendations (6), patients with AIP-1 who are resistant to or cannot tolerate high-dose GC, or have not responded to immunomodulatory therapy (IM), should be given the option of RTX. This monoclonal antibody may be used as an alternate GC medication for induction therapy in patients with confirmed AIP-1. Despite the absence of long-term data, it appears to be a viable steroid-sparing therapy (6).

In a study with a sizable cohort of patients with AIP, Nikolic *et al* (36) examined the effects of RTX therapy in patients with AIP-1. A total of 33.3% of patients entered partial remission, whereas 66.7% of patients entered full remission. Throughout the 17-month follow-up period, no patients relapsed. These findings showed that RTX induces remission and prevents relapse in the treatment of AIP-1 (36).

RTX may be continued as maintenance therapy in a few unique cases. In one study, RTX-assisted induction and maintenance therapy was compared with induction therapy alone in patients with IgG4-RD. Only 11% of individuals who also got RTX as maintenance therapy experienced relapse, compared with 45% of patients treated with RTX as induction therapy (37,38). Patients with biliary disease, indicated by an increase in serum alkaline phosphatase, and a higher IgG4 responder index score (37), an assessment tool that quantifies disease activity and response to treatment based on symptoms, laboratory and imaging findings, and urgency of treatment, have a higher risk of relapse after RTX therapy (37,38).

RTX has also been shown to be an effective treatment for patients who are at a high risk of relapsing, such as those who have multiple organ involvement, have previously experienced relapse, or who have failed disease-modifying anti-rheumatic drug therapy (39). A total of 97% of patients experienced illness response that lasted for 6 months after receiving 2x1,000 mg RTX doses. This demonstrated that RTX therapy is successful in managing illness without co-occurring GCs (39). Due to the lengthy follow-up time of the trial (71 months), a larger percentage of relapse (61%) was observed in patients receiving RTX as maintenance therapy in the study by Backhus *et al* (40). Unlike earlier research, none of the hypothesized risk variables for relapse were discovered (40).

The effectiveness of RTX in leading to remission and treating relapse in IgG4-RD was confirmed, however a substantial relapse rate following therapy (42%) was also found in a French multi-centre study (41). An Italian study investigated the typical relapse period in patients with AIP-1. A total of 80% of RTX-treated patients with recurrent AIP relapsed between year 1 and 3 after beginning therapy, with a median time to relapse of 30 months following the last infusion (42).

RTX was delivered twice (1,000 mg each time 15 days apart) and repeated after 6 months.

Even in patients who have failed prior immunosuppressive therapy, RTX is more effective than other conventional therapies. In patients with recurrent AIP, Soliman *et al* (19) found that RTX had an effectiveness rate of 94%, while that of the other immunomodulators was lower (67%) (19). According to a Mayo Clinic study which had a success rate of 83.3%, individuals with steroid intolerance or IM resistance treated with RTX were able to attain complete remission (43).

It is noteworthy that RTX infusions were repeated in this trial every 2-3 months for a total of 24 months (with a total of 8 extra doses) (43). Serum IgG4 levels drop with a clinical response to RTX treatment, according to Backhus *et al* (40) However, serum IgG4 levels are normal upon presentation in ~20% of patients with AIP-1, therefore IgG4 cannot be used to track treatment (44). In order to reduce infusion responses, premedication with antihistamines, acetaminophen and/or corticosteroids is frequently completed before each dosage of RTX (38,39,45). For RTX treatment, two distinct dose regimens have been suggested: i) 375 mg/m^2 once a week for 4 weeks, followed by maintenance infusions every 2-3 months (oncohematological protocol); and ii) 2x1,000 mg infusions 15 days apart every 6 months (immunological/rheumatoid arthritis protocol) (6).

B-cell depletion therapy with RTX. Janus kinase (JAK) inhibitors represent an emerging class of drugs that have gained increased attention for treating a wide range of autoimmune and inflammatory diseases (46-48), due to their mechanism of action targeting the JAK/STAT signalling pathway involved in regulating immune responses and inflammation. These inhibitors have been studied and used in treating various conditions, including rheumatoid arthritis, psoriasis, UC and various other dermatological diseases, demonstrating efficacy in symptom control and inflammation reduction (46-48).

JAK inhibition in AIP represents an innovative approach, based on understanding the role of JAK/STAT signalling pathways in the specific inflammatory and fibrotic processes of this condition. These pathways are essential in activating pancreatic stellate cells (PSC), which mediate the inflammatory and fibrotic response in pancreatitis. The use of JAK inhibitors, such as ruxolitinib, has shown promising effects in reducing PSC activation, thereby mitigating the symptoms and severity of pancreatitis in experimental models (49).

Particularities of treatment in AIP-2. Treatment for AIP-2 is based on several principles and therapeutic options. AIP-2 is a rare inflammatory disease of the pancreas and differs from IgG4-related AIP-1 in pathological characteristics, epidemiology and risk of relapse (50).

The management approach for AIP involves both alleviating the immediate symptoms of AIP and preventing long-term complications, such as irreversible hepatic fibrosis, and exocrine and endocrine pancreatic insufficiency. This approach considers the clinical manifestations of AIP and the potential association with IgG4-RD, focusing on inducing remission through treatments tailored to every specific case (50).

Steroids are used to induce remission in AIP. ICDC for AIP proposed two distinct types of AIP, AIP-1 and AIP-2. With initial steroid treatment for inducing remission, remission can be successfully induced in almost all subjects with AIP-1 and 2. The relapse rate in AIP-1 is notably higher than that in AIP-2, which has generated a debate on how to effectively treat AIP-1 relapse (23).

Biological therapy, such as anti-tumor necrosis factor (TNF) therapy, is a well-tolerated and effective second-line therapeutic option for AIP-2 relapse or steroid dependency (51).

For a 'definitive' diagnosis of AIP-2, histology is required. In the absence of a 'definitive' histological diagnosis (not performed or inconclusive), the concomitant presence of IBD and an effective response to steroids are required for a 'probable' diagnosis of AIP-2. AIP-2 is a selective pancreatic disease without association with other organs. The lack of validated serological markers makes the diagnosis challenging in clinical practice, particularly in focal forms. A careful evaluation of the clinical profile, especially that of concomitant IBD, associated with accurate imaging, might help in clinical practice to diagnose AIP-2. The response to steroids is crucial to achieving diagnosis in patients without diagnostic histology (52).

4. Discussion

The diagnosis of AIP, an uncommon form of pancreatitis with autoimmune characteristics, is frequently challenging. The two type of AIP, AIP-1 and -2, which are clearly distinguished by ICDC (1), must also be distinguished when AIP is suspected.

Due to the non-specific clinical presentations of both types and the overlap with more serious pathologies such as pancreatic cancer, which can include jaundice, weight loss and abdominal pain in some cases, notable research is needed to develop more precise tools to enable differential diagnosis even in the absence of biopsy (53). To develop new treatment targets and improve the management of the two AIP types, a better knowledge of the etiology of AIP is required. The cornerstone in the development of AIP is the aberrant immune response.

The development of AIP-1 involves both innate and adaptive immunity. The involvement of IgG4 in disease progression is still unknown (54,55), and it is unclear if specific triggers, including changes in the gut flora, can hasten the development of AIP-1. The pathophysiology of AIP-2 is less understood. Steroid medication is the cornerstone of AIP treatment. In the majority of cases with AIP, high dosages of methylprednisolone result in remission. Relapse is prevalent, especially in AIP-1, however because of this, the duration of steroid treatment is still being discussed and alternative therapies are being sought to mitigate their negative effects. Understanding the pathophysiology of the disease will help us identify potential targets for treatment in the future. To maintain remission, steroid-free IM medication such as azathioprine, 6-mercaptopurine or mycophenolate may be employed.

AZA, an immunosuppressant agent used in managing various autoimmune conditions such as rheumatoid arthritis, lupus, Chron's disease and ulcerative colitis, and in the context of transplants, appears to be a useful drug for preventing

relapse in AIP (33), according to reports from numerous cases and small case series (54,55). This association raises marked concerns regarding its safety in patients with AIP (56).

In a case study presented by Venkatesh and Navaneethan (57), a patient with pancreatitis and autoimmune hepatitis developed AZA-induced acute pancreatitis, complicated by a pseudocyst compressing the duodenum, which required surgical intervention. This case highlighted the potential of AZA to cause acute pancreatitis, especially in the presence of preexisting pancreatic disease.

Additionally, Floyd *et al* (58) conducted a population-based study in Denmark, examining the risk of acute pancreatitis in AZA users, including 1,388 patients and 13,836 controls. The results of that study indicated an incidence rate of one case per 659 years of AZA treatment and a relatively increased risk, even after adjusting for confounding factors such as alcohol-related diseases, biliary diseases and GC use.

Another relevant study conducted by Sazonovs *et al* (59) showed an increased incidence of AZA-induced pancreatitis in Crohn's disease compared with that of other diseases. Specifically, 11/224 patients with Crohn's disease experienced acute pancreatitis (4.9%), compared with only 2/129 patients (1.5%) with autoimmune hepatitis. This suggests that acute pancreatitis is strongly associated with Crohn's disease and rarely occurs in other underlying conditions.

Current data suggest that the use of AZA in this patient population should be approached with caution, considering the specific condition and medical history of every patient (32,59). Further studies are needed to better assess the risks and benefits of AZA in the treatment of AIP and to develop management strategies that maximize therapeutic benefits while minimizing potential risks. B-cell depletion therapy with RTX demonstrated a solid immunologic basis and was an efficient method for both producing and maintaining illness remission and treating relapse. RTX is an efficient medication for the treatment of recurrence in patients with corticosteroid intolerance and ensures total remission in ≤83% of patients (60-62).

The latest development in the management of both types of AIP is immunotherapy. Anti-TNF antibodies as well as RTX can be used to treat steroid-resistant variants of AIP-1 and relapse (63,64). Although relapse is substantially less frequent following steroid treatment than in AIP-1 (27), anti-TNFα appears to be beneficial in AIP-2 (65).

In the context of targeting the JAK/STAT signalling pathways, *in vitro* and *in vivo* studies have provided solid evidence regarding the ability of JAK/STAT inhibition to reduce STAT3 phosphorylation and suppress cellular proliferation. This finding is of crucial importance, especially since JAK inhibitors are already well tolerated and have been approved for treating other inflammatory conditions. Although the use of JAK inhibitors in the treatment of patients with AIP has not yet been subjected to formal clinical studies, preliminary results suggest a notable therapeutic potential (66-68). Therefore, JAK/STAT inhibition represents a promising therapeutic direction for addressing AIP, and future research in this area is essential to confirm the effectiveness and safety of this therapeutic strategy. This approach opens up prospects for developing more effective and personalized treatment strategies for patients with AIP.

The literature on the use of novel biologic drugs to treat AIP-2 is constrained to particular circumstances.

5. Conclusions

AIP is a challenging nosological condition to diagnose and treat. Finding reliable biomarkers and efficient treatments can be supported by understanding the disease pathogenesis. In the majority of cases, the treatments that are currently available are effective. However, in the era of immunotherapy and personalized medicine, additional research should be carried out to develop drugs that work as well as corticosteroids in initiating and maintaining remission or treating relapse, but with a different mechanism of action. Future research should concentrate on finding novel biomarkers that will enable more precise diagnosis, better classification of the various forms of AIP and tailored treatment with fewer side effects.

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Authors' contributions

VP, MMR, AND, DR, DD, RP and MCF analysed the data, and wrote and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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