Diagnosis and treatment of autoimmune pancreatitis

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Purpose of review
Clinical management of autoimmune pancreatitis changed over the last years. The lack of high-quality studies, probably due to the relative rarity of the disease, has not fully clarified many diagnostic and therapeutic aspects. Aim of this review is to overview the literature from a clinical point of view, focusing on diagnostic and therapeutic approach to this complicated disease.

Recent findings
They have been focused mainly on the risk of misdiagnosing a cancer. Many significant articles have been published on the treatment strategies of autoimmune pancreatitis, considering both induction and maintenance therapy.

Summary
Diagnosis of autoimmune pancreatitis remains challenging, particularly in focal pancreatic involvement, despite recent advances on imaging modalities. Treatment is based on induction and maintenance phases. Steroid treatment remains the best option to induce remission. Maintenance therapy may be used to prevent disease relapses, and low-dose steroids, azathioprine or rituximab are the therapeutic options. However, it remains unclear which patient needs to be treated.

Keywords
autoimmune pancreatitis, azathioprine, diagnosis, rituximab, steroids, therapy

INTRODUCTION

Autoimmune pancreatitis (AIP) is a fibroinflammatory disease that may involve the pancreas diffusely (diffuse form) or focally (focal form).

Two different histological subtypes (type 1 and type 2) have been defined according to Honolulu consensus [1]. The diagnosis of AIP subtypes may be achieved by International Consensus Diagnostic Criteria (ICDC) even in the absence of histology [2]. This consensus introduced a third subtype, not otherwise specified (NOS) when type 1 or 2 cannot be diagnosed.

Type 1 AIP is considered part of IgG4-related disease (IgG4-RD) and is the most frequent subtype observed especially in Eastern countries, affecting patients in the sixth to seventh decade of life. It is characterized by high risk of recurrence after steroid treatment, high other organs involvement rate (proximal biliary system, kidney, retroperitoneum, salivary glands), elevation of serum IgG4.

Type 2 AIP accounts for around 10–20% of AIP patients in western countries (less than 5% in Eastern countries), affecting younger patients than type 1 (third to fourth decade). It has no serum IgG4 elevation, low risk of recurrence and no other (extrapancreatic) organ involvement except for inflammatory bowel disease [3].

In rare cases, AIP may affect paediatric population [4▪], but very few cases are reported in the literature and the clinical profile described in children seems like type 2, generally characterized by the absence of both serum IgG4 elevation and extrapancreatic organ involvement.

Despite the clinical, serological and prognostic differences between AIP type 1 and 2, both subtypes share a dramatic response to steroids. However, Kubota *et al.* [5▪] described a relatively large retrospective series of AIP type 1 patients who experienced a spontaneous remission of the disease without steroid treatment.

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KEY POINTS

- Differential diagnosis between focal AIP and cancer is still the most challenging diagnostic step in clinical practice.
- Close follow-up is needed during induction therapy to monitor the radiological response and reduce the risk of misdiagnosing cancer.
- Therapeutic approach is based on induction therapy (high-dose steroids) and maintenance therapy (low-dose long-term steroids, azathioprine, rituximab).
- Maintenance therapy seems to be effective in reducing the risk of disease relapses.
- A step-up approach may be suggested for maintenance therapy, to select patients for a correct off-label use of rituximab.

AIP type 1 and 2 are not distinguishable at imaging, but the classification in subtypes is clinically important because type 1 is generally a more aggressive disease with a high risk of synchronous or metacronous involvement of extrapancreatic organs and a high risk of relapse. No definitive data have been published on risk factors for predicting the risk of disease relapse in type 1 AIP. However, some criteria are reported in a recent International Consensus for the treatment of AIP [6▪▪]. The presence of one or more of the following criteria allows to consider patients at high risk of relapse: diffuse pancreatic enlargement at diagnosis, slow response to steroids, high level of serum IgG4 after induction therapy, more than one extrapancreatic organ involvement and proximal (intrahepatic) IgG4-sclerosing cholangitis. Some of these criteria have been confirmed by recent published articles that reported other organ involvement with proximal bile duct as the strongest factor predicting the disease relapse [7] and the relative rise of serum IgG4 levels after steroid therapy as a useful indicator of relapse [8].

In the present review, an extensive research was performed on PubMed using AIP or IgG4-related disease as search parameters, limiting the period from 1 January 2017 to 31 March 2018. We found 101 articles in AIP and 189 in IgG4-related disease. The most clinically relevant articles for diagnosis and therapy of AIP were then selected and discussed.

DIAGNOSIS

The diagnosis of AIP is the most challenging aspect in clinical practice. The ICDC are the worldwide accepted criteria to diagnose AIP [2].

In diffuse form, diagnosis is generally easy with typical imaging features. Potential differential diagnosis is pancreatic lymphoma, extremely rare, and acute pancreatitis, which has a different clinical presentation. In this clinical scenario, standard imaging procedures [computed tomography (CT) scan and MRI-MRCP sequences] show a diffuse enlargement of the pancreas ('sausage-like'), retention of contrast medium in late phase and sometimes a capsule like-rim. Tissue sampling in these patients is generally not required.

The real issue in clinical practice is the diagnosis of focal AIP because the risk of misdiagnosing a neoplasia is high. A correct diagnosis is crucial to avoid pancreatic resections in inflammatory masses and steroid treatment in cancers. The differential diagnosis is extremely challenging in the absence of extrapancreatic involvement or serum IgG4 elevation. Therefore, new serological markers and/or pancreatic biopsy are important tools to make a correct diagnosis in this clinical setting.

Ghassem Zadeh *et al.* [9] recently published a study showing different cytokine profiles in AIP and cancer. However, these data need to be confirmed and only serum IgG4 are actually available for the diagnosis of AIP type 1 and none for type 2. A recent meta-analysis [10] found that serum IgG4 with a cut off 130–140 mg/dl has 70% sensitivity and 95% specificity comparing AIP with pancreatic cancer. These data seem to be confirmed by Pak *et al.* [11] who analysed 298 resected patients for hepatobiliary diseases, including 52 AIP patients, and reported 67% sensitivity and 96% specificity, using a serum IgG4 cut off of 135 mg/dl. However, positive predictive value was only 80%, and 9% of pancreatic adenocarcinoma had serum IgG4 elevation. Therefore, pancreatic mass associated with high serum IgG4 is not pathognomonic of AIP. Moreover, Macinga *et al.* [12] reported a histological diagnosis of AIP in 15 patients (5.1%) in a retrospective series of 295 patients resected for focal pancreatic mass, six of whom (40%) with a concomitant pancreatic adenocarcinoma. A close instrumental follow-up is therefore suggested at 3–4 weeks after steroids.

Endoscopic ultrasound (EUS) with fine needle aspiration biopsy (FNB) or cytology (FNAC) has been proposed as cardinal technique for the diagnosis of AIP. In the last years, contrast-enhanced EUS and quantitative elastography EUS have been proposed as additional tools to differentiate neoplastic and inflammatory masses with a good sensitivity and specificity [13]. However, in the clinical scenario of a pancreatic mass, a pretest probability of AIP is quite low (less than 10%) and of pancreatic adenocarcinoma very high (>90%). Kanno *et al.* [14] reported a histological diagnosis of AIP in only 57% of cases in

a prospective multicentre study enrolling 78 patients with imaging highly suggestive for AIP. Sensitivity of EUS-FNAB in pancreatic adenocarcinoma is quite high (97%) [15]. Therefore, EUS-FNAC may be useful mainly to exclude cancer in patients with suspected AIP, before using steroids.

The availability of new needles in clinical practice shows encouraging preliminary results not only for the diagnosis of AIP but also to differentiate type 1 and type 2 [16].

Finally, a growing interest is focused on the role of 18F-fluorodeoxyglucose PET/CT (^{18}F-FDG PET/CT) in differentiating AIP from pancreatic cancer [17,18]. As expected, AIP is characterized by an increased FDG metabolic activity. AIP patients have more frequently a diffuse increased FDG metabolic activity than patients with pancreatic cancer. In focal forms, ^{18}F-FDG PET/CT may be helpful to detect extrapancreatic organs involvement suggesting a systemic IgG4-related disease.

TREATMENT

Induction therapy

Steroids are the gold standard therapy for AIP (independently from the subtype) and a clinical and radiological response to steroids is considered a cardinal criterion for the diagnosis of AIP based on the ICDC [2]. In focal forms, the lack of response to steroids should suggest a diagnosis of cancer and surgical resection is mandatory.

However, despite the worldwide acceptance of steroids as standard induction therapy, no definitive data have been published on dosage, duration and tapering. In 2017, an International Consensus for the treatment of AIP has been published [6▪▪]. The consensus stated that the initial dose should range from 0.6 to 1 mg/kg/day. Radiological response should be assessed 2–4 weeks after starting steroid therapy, preferably with the same imaging technique used for the pretreatment diagnosis. Moreover, applying ICDC, a conclusive diagnosis of AIP is reached in some cases only after assessing the response to steroids. Once the response is assessed, steroids should be tapered by 5–10 mg per week. In Europe and United States, steroids are stopped after tapering, while in Eastern countries are stably maintained at dose of 2.5–5 mg per day up to 2 years to reduce the risk of relapse [19▪▪,20].

There is no indication for the use of immunosuppressants as induction therapy, because azathioprine, the most used in AIP, reaches therapeutic efficacy only after 2–3 months. Rituximab, an anti-CD20 biologic agent, is the only alternative drug proposed to induce remission in AIP type 1 patients not or slow responders to first-line steroids or with contraindications to steroids [6▪▪]. Rituximab cannot be used in AIP type 2 and type NOS.

Maintenance therapy

The aim of maintenance therapy is to reduce the incidence of relapses. Selection of patients to be treated and choice of the most appropriated drug are crucial in clinical practice.

The first clinical point is to define patients to be treated with maintenance therapy. No definitive criteria have been defined yet, with a large heterogeneity of patients treated in published articles. In Eastern countries, where AIP type 1 is the largely predominant form (more than 90%), every single patient is treated with a maintenance therapy after inducing remission for up to 2 years. However, considering that after remission around 40% of patients will never experience a relapse, there is a considerable risk of overtreatment. The international consensus [6▪▪] stated that maintenance therapy may be useful in some patients with AIP type 1, without defining definitive selection criteria. As the incidence of relapse is quite variable in type 1, a less aggressive approach may be to introduce maintenance therapy only after disease relapse to avoid overtreatment.

Three different drugs are available: low-dose steroids, azathioprine and rituximab.

In Eastern countries, a low-dose maintenance therapy is proposed to all AIP type 1 patients according to their high risk of relapse. Masamune *et al.* [19▪▪] showed the efficacy of this strategy publishing a randomized controlled trial on the role of low-dose steroids as maintenance therapy in AIP. All 49 patients included in the study were treated with prednisolone 0.6 mg/kg to induce remission. After tapering the dose to 5–7.5 mg/day, the authors showed that patients who continued the therapy up to 3 years had significantly less relapses (23.3%) compared with patients who discontinued therapy after 26 weeks (57.9%). Despite this is the only controlled trial in AIP, many limitations have been stressed, summarized in a recent editorial [20]. However, a retrospective study involving 510 patients seems to confirm these data [21].

In western countries, the use of immunosuppressants is generally preferred to avoid the adverse events of the long-term use of steroids. The most studied drug is azathioprine, which is generally administered at a dose of 2–2.5 mg/kg. Azathioprine maintained 75% of treated patients in sustained remission at 3 years [22▪]. These data are significant

because obtained in patients who already experienced a previous relapse.

Low-dose steroids and azathioprine might be used as maintenance therapy in both type 1 and type 2 AIP.

The third therapeutic option, which is still off-label and limited to type 1 AIP, is rituximab. A recent article published by the Mayo Clinic group [23▪] reported 43 patients treated with rituximab as induction therapy. Those patients who received induction followed by maintenance therapy with rituximab had a significantly lower relapse rate at 3 years (11%) than those who received only induction with rituximab without a subsequent maintenance therapy (45%).

Overall, maintenance therapy seems to be effective in reducing the disease relapse. A step-up approach is probably rational. Treatment based on low-dose steroids (prednisone 5 mg/day) is probably the most largely applicable, well tolerated, cheap and the only evidence-based. Azathioprine seems to be an effective cheap alternative. Its use should be probably limited in older patients, for the age-related risk of cancer. Rituximab can be actually considered as second-line treatment in patients relapsing during low-dose steroids or azathioprine maintenance therapy.

CONCLUSION

Diagnosis of AIP is still difficult in some cases and the risk of misdiagnosis of cancer remains a bugbear. The lack of a specific serum marker does not allow to treat safely patients affected by AIP. Pancreatic biopsy is strongly suggested in focal pancreatic involvement, as well as an imaging assessment at 3–4 weeks after steroids, in both diffuse and focal forms.

Induction of remission is based on steroids, but optimal dosage and timing of tapering is not yet well defined, due to lack of controlled trials. Maintenance therapy may be used in relapsing disease, and low dosage steroids is the only evidence-based on a recent and criticized controlled trial. Azathioprine and rituximab are the other options, but evidence is still unsatisfactory.

Treatment of patients suffering from AIP remains difficult, requires follow-up and should be based on many parameters such as type of the disease, extrapancreatic involvement, age, comorbidity and patient's preference of cure. For all these reasons, therapy should be managed carefully in experienced centres.

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Conflicts of interest

Luca Frulloni received honoraria from Abbvie and Mylan. This conflict of interest did not impact in the present article.
The remaining authors have no conflicts of interest.

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- ▪ of special interest
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