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Update on Autoimmune Pancreatitis and IgG4-Related Disease

Marco Lanzillotta[1,2] | Miroslav Vujasinovic[3,4] | Johannes-Matthias Löhr[3,4] | Emanuel Della torre[1,2]

[1]IRCCS San Raffaele Scientific Institute, Università Vita-Salute San Raffaele, Milan, Italy | [2]Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UNIRAR), IRCCS San Raffaele Scientific Institute, Milan, Italy | [3]Department of Upper Digestive Diseases, Karolinska University Hospital, Stockholm, Sweden | [4]Department of Clinical Science, Intervention, and Technology (CLINTEC), Karolinska Institute, Stockholm, Sweden

Correspondence: Marco Lanzillotta (lanzillotta.marco@hsr.it)

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ABSTRACT

Autoimmune pancreatitis is an increasingly recognized inflammatory type of subacute pancreatitis; two subtypes of autoimmune pancreatitis have been identified so far: the "lymphoplasmacytic" type 1 variant and the "neutrophilic" type 2 variant. Type 1 autoimmune pancreatitis represents the most common manifestation of IgG4-related disease, a fibro-inflammatory disorder characterized by elevated IgG4 levels in the serum and affected tissues. Type 2 autoimmune pancreatitis is a pancreas-specific disorder that frequently occurs in the context of inflammatory bowel diseases. Due to the complexity of both diseases, a comprehensive work up with imaging, laboratory, and histological studies is required to achieve a diagnosis and rule out malignancies. Glucocorticoids represent the cornerstone of the treatment, often supported by other immunosuppressive drugs in case of steroid intolerance or aggressive disease. Maintenance treatment is often employed in type 1 autoimmune pancreatitis because of the higher relapse rate compared with type 2 autoimmune pancreatitis. In this review, we summarize the key concept of autoimmune pancreatitis, delve into the differential diagnosis between the two subtypes, and cover the recent relevant research findings and pressing unmet needs.

1 | Introduction

Autoimmune pancreatitis (AIP) is an inflammatory disease of the pancreas that can lead to chronic pancreatitis. The term AIP was first coined 30 years ago by Yoshida et al. upon the evidence of an immune-mediated steroid-responsive form of chronic pancreatitis [1]. This concept further evolved in two different entities in the following 2 decades, namely type 1 and type 2 AIP. The former directly stems from the seminal findings of Japanese investigators [2, 3] who unveiled the link between serum IgG4 levels and the so called "lymphoplasmacytic pancreatitis" [4]. Indeed, type 1 AIP is now considered the most frequent manifestation of IgG4-related disease, a multi-organ fibro-inflammatory disorder characterized by dense lymphoplasmacytic infiltrate and storiform fibrosis in the affected organs that typically involves elderly males [5–7]. On the contrary, type 2 AIP emerged as a distinct entity in the early 2000s after acknowledging a different pathological scenario featured by neutrophilic infiltration within the lumen and epithelium of the interlobular ducts a finding designated as "granulocyte epithelial lesion" (GEL) [8, 9]. In contrast to type 1 AIP, type 2 AIP is limited to the pancreas and involves younger patients with no sex predominance.

2 | Epidemiology

The incidence and prevalence of AIP are rising likely due to an increasing awareness of the disease. Data from a population study

performed in Japan showed that the incidence of type 1 AIP increased from 0.8 to 3.1 cases per 100,000 people between 2007 and 2016, reflecting an overall prevalence rate of 10/100,000 individuals [10]. Although no epidemiological data are available in Europe, it is estimated that AIP accounts for 6% of cases of all forms of chronic pancreatitis (prevalence of 10–40 cases per 100,000 individuals) [7, 11, 12]. This points to a prevalence of AIP of 1–2 cases per 100,000 individuals, slightly lower compared to Japanese estimates [10]. A recent study from Wallace ZS et al. reported an incidence and prevalence of IgG4-RD in the USA of 1.39 per 100,000 person-years and of 5.3/100,000 persons, respectively [13]. Scant data are available on the epidemiology of type 2 AIP due to its rarity and more complicated diagnosis [14]. Overall, type 2 AIP appears more prevalent in western countries [15, 16]. In the largest cohort ever published on AIP, the percentage of type 2 AIP over the total AIP cases was 14% in the United States, 13% in Europe, and 4% in Asia [17].

3 | Clinical Manifestations and Other Organ Involvement (OOI)

The clinical presentation of type 1 and type 2 AIP is often undistinguishable and depends on the distribution and extent of the pancreatic gland involvement. AIP involving the pancreatic head or the entire gland, for instance, may lead to obstructive jaundice and abdominal pain, whereas involvement of the uncinate process may be incidentally discovered. Additional manifestations may include signs and symptoms of endocrine and exocrine pancreatic insufficiency, such as steatorrhea, postprandial bloating, increased stool frequency, and weight loss [7, 18–20].

Notably, type 1 AIP more commonly presents insidiously with a relapsing remitting course that ultimately leads to chronic pancreatitis. On the other hand, the onset of type 2 AIP is typically acute (10%–63%) [17], yet without local or systemic complications [21]. Accordingly, weight loss, signs of endocrine and exocrine insufficiency, and jaundice are more frequently observed in type 1 AIP [15, 22].

The evidence of other organ involvement (OOI) in addition to the pancreas is considered an important diagnostic tool by the AIP diagnostic guidelines published so far [23, 24]. Indeed, the **O** in the acronym HIS**O**Rt (Histology, Imaging, Serology, Other organ involvement, Response to treatment) stands for "other organ involvement", emphasizing the importance of extra-pancreatic disease in the overall assessment of disease burden. OOI gained even more importance in 2011 after the publication of the International Consensus Diagnostic Criteria (ICDC) for Autoimmune Pancreatitis, in which OOI represents an important diagnostic criterion and is pivotal in distinguishing between type 1 AIP and type 2 AIP [23].

OOI has been reported in 61%–95% of patients with type 1 AIP - either synchronous or metachronous with respect to pancreatic involvement—in the form of different extra pancreatic manifestations of IgG4-RD [25–28]. These include IgG4-related cholangitis [24, 25, 28], tubulointerstitial nephritis [29, 30], lung disease [31, 32], orbital pseudotumor [18], sialadenitis [18, 26, 27], thyroiditis [18, 26, 27], aortitis [18, 27, 31], retroperitoneal fibrosis [18, 26, 27], and sinonasal lesions [19] (Figure 1). Signs and symptoms related to OOI by IgG4-RD directly stem from the enlargement of the targeted organs, often leading to the compression of adjacent structures, such as ureters and optic nerves in case of retroperitoneum and orbital involvement, respectively [18].

OOI in case of type 2 AIP mainly includes inflammatory bowel diseases (IBD) and the tight relationship between these two conditions has been progressively acknowledged within the ICDC [23]. An international study on 35 patients with type 2 AIP showed IBD in 82.8% of patients [33] and an Italian study reported a similar IBD rate (87.5%) in a large monocentric Italian cohort [15]. Remarkably, all IBD cases were ulcerative colitis, occurring either synchronous (34%) or metachronous (66%) to AIP, whereas no cases of Crohn's disease were reported [15].

4 | Diagnosis

The diagnosis of AIP requires the exclusion of pancreatic ductal adenocarcinoma (PDAC), the most important mimicker of autoimmune pancreatitis. Distinction between type 1 and type 2 AIP is also important as the long-term outcomes and management strategies differ between these two entities.

As stated by the different set of available guidelines, the diagnosis of AIP builds upon clinical, laboratory, histological, and radiological features [23, 34]. Cross-sectional imaging is of paramount importance in AIP diagnosis and might be sufficient for diagnosis in the presence of typical findings and either IgG4 elevation or other organ involvement. On computed tomography (CT) images, typical AIP shows diffuse enlargement of the pancreas with delayed enhancement ("sausage pancreas") in association with a capsule-like low-density rim ("halo sign") and strictures of the main pancreatic duct (> 1/3 of the length or multifocal) [17, 23, 34]. On the contrary, pancreatic necrosis and pancreatic duct dilation, point toward other diagnoses. Magnetic resonance imaging (MRI) findings suggestive of AIP include decreased signal intensity in T1 sequences as well as diffusion restriction with high diffusion-weighted imaging (DWI) signal [34]. Moreover, 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) scan is emerging as a new tool for AIP longitudinal follow up being able to capture multi-organ involvement monitoring disease activity, but fails to distinguish between AIP and PDAC [35]. Unfortunately, the distinction between type 1 and type 2 AIP cannot rely on imaging findings that are indeed shared by the two entities, even though capsule-like rim and thickening and enhancement of the intrapancreatic bile duct are less common in type 2 AIP [14].

Endoscopic ultrasound represents a powerful tool to aid AIP diagnosis, unveiling typical features such as diffuse hypoechoic pancreatic enlargement and/or biliary tree thickening and allowing histological confirmation via core biopsy (19-gauge needle preferred over the 22 gauge) [7, 36].

Histopathology is key in subtyping AIP and achieving a definite diagnosis. Although both entities are characterized by dense

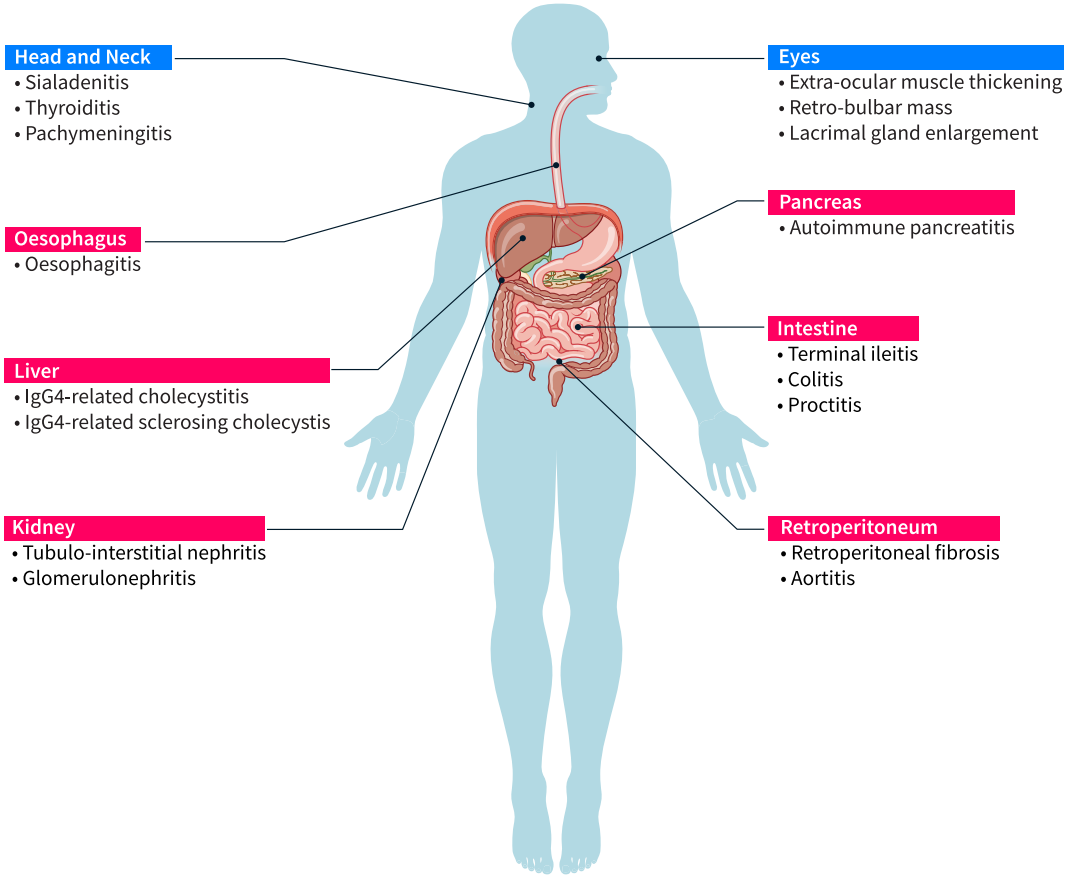

FIGURE 1 | Sites of other organ involvement (OOI) in IgG4-RD. Highlighted are the manifestations in the gastrointestinal tract. Modified from [34].

inflammatory infiltrates, the location and the component of the inflammatory burden differ between the two entities. While type 1 AIP shows a lobule centric lymphoplasmacytic infiltrate rich in IgG4+ plasma cells interspersed in storiform fibrosis, type 2 AIP typically displays a periductal neutrophils rich infiltrate also known as GELs [23, 37]. However, in line with ICDC guidelines, we proceed with a core pancreatic biopsy in patients presenting atypical radiological or laboratory findings, while we usually perform a fine needle aspiration to exclude the presence of malignant cells in patients with classic AIP features such as "sausage-shaped pancreas" or very high serum IgG4 levels [23].

Serum biomarkers might nudge toward AIP diagnosis in the setting of classic imaging findings, but they are largely non-specific [38]. Inflammatory markers are usually normal or slightly elevated in both forms of AIP. Serum IgG4 levels are elevated in 60%–70% of type 1 AIP patients and correlate with the number of organs involved by IgG4-RD, whereas they are typically normal in type 2 AIP (Figure 2) [39]. Other laboratory findings suggestive of type 1 AIP include eosinophilia, elevated IgE level, and polyclonal hypergammaglobulinemia [40–42]. On the contrary, no biomarkers are available in type 2 AIP even though anti-neutrophil cytoplasmic antibodies, anti-lactoferrin, and anti-carbonic anhydrase antibodies can be detected, especially in patients with concomitant ulcerative colitis [14, 33, 43, 44]. Thus, building upon the tight correlation between type 2 AIP and IBD, a probable diagnosis can be made in the presence of this association, while a definite diagnosis requires histopathological confirmation [23].

Finally, response to glucocorticoids (GCs) represents an additional item to confirm AIP diagnosis, especially in patients presenting with typical laboratory, imaging, and clinical features. Notably, it should be administered only after a negative work up for PDAC. A positive response to (GCs)entails a resolution or marked improvement of pancreatic and bile duct abnormalities after 2 weeks of prednisone 0.6–1 mg/kg [23, 34].

5 | Treatment Options

Several treatment guidelines have been published since AIP appraisal and its acknowledgment within the IgG4-RD spectrum [34, 45, 46].

The ICDC guidelines recommend AIP treatment for all symptomatic patients and for asymptomatic patients with (I) persistent pancreatic focal mass at imaging, (III) liver test abnormalities in case of concomitant IgG4-related cholangitis, or (III) subclinical situations that could lead to irreversible organ failure [34, 46]. It is still debated whether prompt treatment alters the progression toward chronic pancreatitis [47, 48].

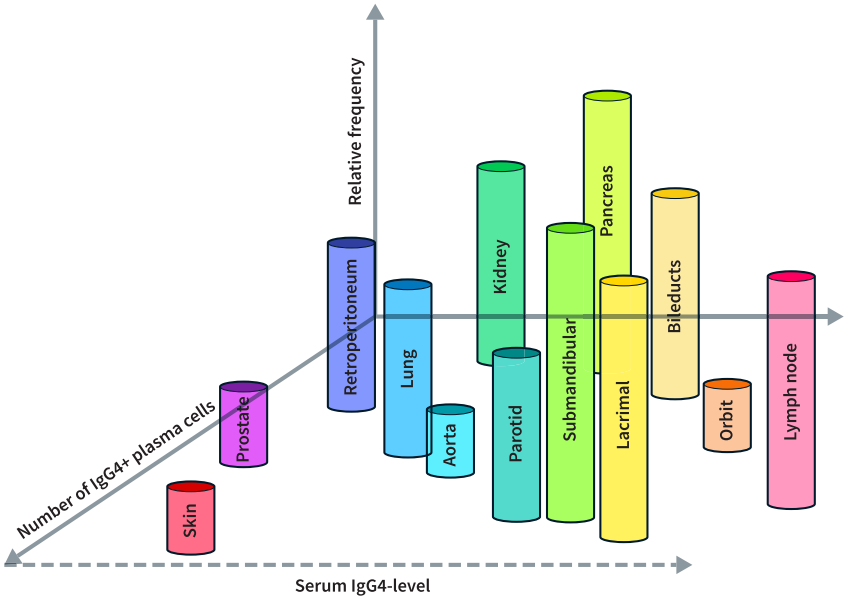

FIGURE 2 | The levels of IgG4 in blood and tissue and the frequency is varying in different other organ involvements (OOI). Adapted from [7].

GCs represent first-line therapy for induction of remission owing to the high rate of remission (95%–100% according to the described cohorts) [17, 18, 46, 49]. Suggested prednisone starting dose ranges between 0.6 and 0.8 mg/kg for 2–4 weeks [34, 50]. Upon confirmation of response to treatment (2–4 weeks after treatment start), GCs are then tapered by 5 mg every 2 weeks and discontinued after 3–6 months [34, 46]. However, several studies, including one randomized trial, highlighted the importance of maintenance treatment to prevent type 1 AIP relapse that can peak to 70% [17, 49, 51–53]. Indeed, maintenance treatment should be considered in those patients at higher risk of relapse, such as patients with previous relapses, proximal biliary tree involvement, multi-organ involvement, and very high baseline IgG4 level [34]. As such, Culver et al. showed that serum IgG4 level of ≥ 2.8 g/L at diagnosis (1.4 g/L upper limit of normal for serum IgG4), as well as a level of IgE at diagnosis > 380 kIU/Lwere associated with relapse, with higher values tied to higher relapse risk [41, 54]. In addition, Cho et al. showed that proximal and distal IgG4-related biliary tree involvement exhibited different long-term outcomes, being the former associated with significantly higher risk of relapse [55]. In addition, patients in whom a relapse would pose the risk of organ failure benefit from prolonged treatment [34].

In a pan-European retrospective study of 735 patients with type 1 IgG4-related AIP, Overbeek et al. reported that induction of remission treatment with higher (≥ 0.4 mg/kg/day) corticosteroid doses was no more effective than lower (< 0.4 mg/kg/day) doses [16, 49] in terms of achieving complete remission. Similarly, maintaining the initial dose of glucocorticoids for more than 2 weeks was no more effective than a shorter course of therapy (< 2 weeks) in inducing remission. In addition, induction of remission was independent of the steroid-tapering duration and total cumulative steroid dose [18]. These results confirm the finding from Buijs et al. that highlighted a similar response rate in patients treated with low dose GCs (< 20 mg die) compared to high dose GCs (> 40 mg die) [56]. Overall, these data reflect the high sensitivity of IgG4-RD to glucocorticoids and suggest that aggressive corticoids regimens might add no additional advantages over lower doses still exposing patients to higher steroid toxicity [13].

In order to mitigate the relapse risk, several strategies have been employed, such as low dose GCs, immunosuppressive drugs, and rituximab [5, 34, 57]. Masamune et al. showed in a randomized controlled trial (RCT) the superiority of long-term (3 years) low-dose GCs compared to induction treatment alone [52]. However, prolonged GCs therapy might worsen metabolic outcomes in an already frail population [42, 58]. Immunosuppressive drugs (DMARDs) are usually employed on top of GCs and include azathioprine, mycophenolate mofetil, methotrexate, leflunomide, tacrolimus, ciclosporin A, iguratimod, and cyclophosphamide ([59–64]). The rationale for DMARDs use is to lower the cumulative GCs dosage, improve remission rate, and reduce relapse rate compared to GCs alone, as demonstrated by two prospective trials and one meta-analysis [60, 61, 65]. Lastly, owing to the pivotal role of B cells in IgG4-RD, B cells depletion therapy with rituximab (either 375 mg/m^2 weekly for 4 weeks or two 1000 mg infusions 15 days apart) was shown to lead to a high remission rate even without concomitant GCs in multiple international cohorts [26, 66–71]. This strategy should thus be considered in patients with GCs intolerance, GCs resistance, or multiple relapses [34, 72]. Interestingly, several retrospective studies and a recently released meta-analysis unveiled a lower relapse rate in patients maintained on periodical rituximab infusions and demonstrated that monitoring total CD19 cells and memory B cells in the peripheral blood might help predict the recurrence of AIP and instruct on the correct pacing of rituximab infusions alone [73–76]. Based on the evidence of the efficacy of B-cell depletion therapy in patients with IgG4-RD, two RCTs are ongoing to investigate the role of other B-cell depleting agents in type 1 AIP treatment, such as inebilizumab and obexelimab [77, 78]. An algorithm for the treatment of type 1 AIP is reported in Figure 3.

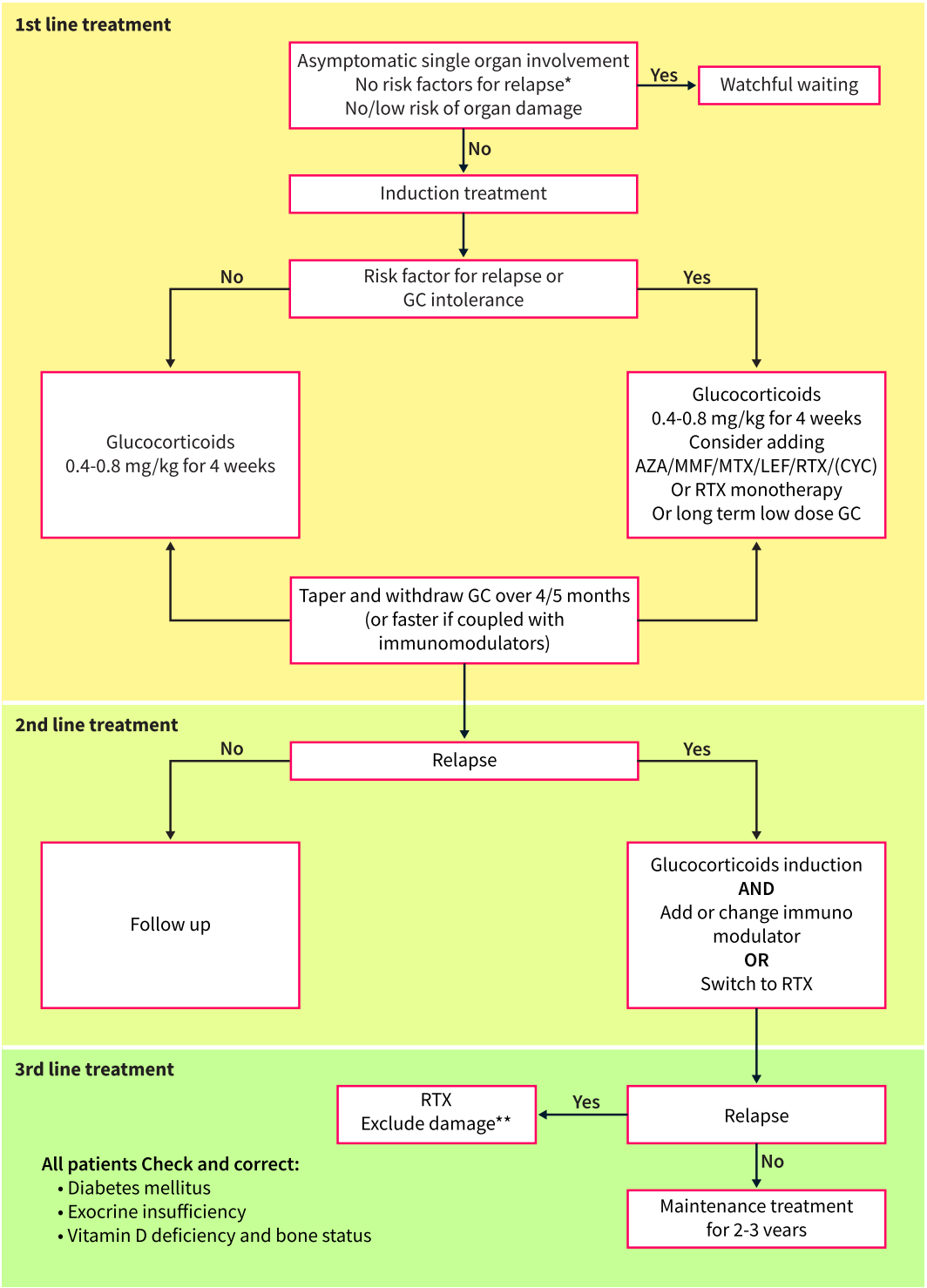

FIGURE 3 | Type 1 AIP treatment algorithm. AZA: azathioprine; CYC: cyclophosphamide; LEF: leflunomide; MMF: mycophenolate mofetil; MTX: methotrexate; RTX: rituximab. *Previous relapses; very high serum IgG4 at baseline; very high IgE at baseline; multiorgan involvement; proximal biliary tree involvement. **Damage is not reverted by immunosuppressive treatment.

Because of the lower relapse rate in type 2 AIP, its induction treatment largely resembles that of type 1 AIP without the need for maintenance treatment. In selected patients with concomitant IBD, TNF-alfa inhibitors and anti IL12/23 antibodies proved successful in prompting AIP remission [79, 80]. In a small case series, colchicine managed to maintain remission in patients with relapsing type 2 AIP, underscoring the key role of neutrophils in this disease [81].

6 | Novel Research Findings and Unmet Needs

Since its first conceptualization in the early 1990s, much has been learned about AIP and most clinical, diagnostic, and therapeutic challenges in the field have been outlined in the present review [1]. However, there are several unmet needs that deserve future research and urgent response to comprehensively ameliorate patients' management.

The most pressing ones are related to diagnostic resources and treatment. The diagnosis of autoimmune pancreatitis often relies on expert opinion, with referral centers offering multidisciplinary teams with experience in this disease. Differentiation between mass-forming AIP and malignancy as well as between type 1 and type 2 AIP, for instance, remains a challenge to clinicians, and more diagnostic modalities that better discriminate these entities are needed. Although certain autoantibodies have been associated with AIP, autoantibodies specific for type 1 and type 2 AIP, that can be leveraged for diagnostic purposes, are lacking [82]. Accordingly, there is a need for dynamic biomarkers that can reveal the activity of the immune response for the longitudinal care of patients before organs are damaged. Similar to the diagnostic gap, there is no therapy approved for the induction or maintenance of remission of either form of AIP. In particular, although AIP typically promptly responds to glucocorticoids, we currently lack mechanistic treatments that might avoid short- and long-term steroid-related side effects. Indeed, B-cell depletion strategies as well as anti-neutrophils and IL-12/23 therapies have been proposed for type 1 and type 2 AIP, respectively [80, 81], but we currently ignore the optimal dosage, frequency of administration, and treatment duration. These are urgent needs that will be hopefully addressed by ongoing and future trials. Finally, evidence in favor of an autoimmune origin of AIP is controversial because auto-reactive B and T cells as well as autoantibodies capable of inducing pancreatic damage have not been clearly identified.

In this regard, a number of recent studies might lead the way toward a better understanding of the pathophysiology of autoimmune pancreatitis and its management [15, 18, 83, 84]. Shiokawa et al. identified an autoantibody against pancreatic laminin 511-E8 in up to 50% of patients with type 1 IgG4-related AIP. Mice immunized with human laminin 511-E8 induced antibodies and pancreatic injury fulfilling the pathologic criteria for human AIP [75]. Moreover, Trampert et al. unveiled the cytoprotective role of laminin 511, enhancing cholangiocellular barrier function and ultimately preventing bile acid-induced apoptosis [85]. In parallel, Hubers et al. identified specific IgG1 and IgG4 autoantibodies targeting annexin A11 in patients with AIP or IgG4-related cholangitis. Annexin A11 is a key component of bile duct homeostasis, leading to the formation of "biliary bicarbonate umbrella," preventing bile acid-mediated damage [86]. Binding of annexin A11 autoantibodies inhibits annexin A11 function, thus ultimately contributing to bile duct damage [87]. Notably, IgG1 and IgG4 autoantibodies shared annexin A11 epitopes, the latter being able to block the binding of IgG1 antibodies. In this view, IgG1-mediated pro-inflammatory autoreactivity against annexin A11 could be dampened by annexin A11-specific IgG4 antibodies, supporting an anti-inflammatory role of IgG4 in IgG4-RD [86, 87].

Similarly, Kurashima et al. identified glycoprotein 2 (GP2) as a potential auto-antigen of type 2 AIP. GP2 is expressed at pancreatic and intestinal levels as part of the "pancreas-intestinal barrier axis" acting as a first defense against adhesive and invasive commensal bacteria. GP2 expression is induced by TNFalfa and correlates with intestinal inflammation in patients with Crohn's disease. Because pancreas-specific GP2-deficient mice have more severe intestinal inflammation, anti GP2 autoantibodies might phenocopy the genetic defect and establish a link between IBD and type 2 AIP in humans [83]. The discovery of these autoantibodies should aid in the understanding of AIP pathogenesis and possibly improve the diagnostic process.

From a clinical perspective, a recent study clarified some relevant epidemiological and therapeutic features of type 2 AIP. Indeed, in the largest type 2 AIP cohort reported to date with a mean follow-up of nearly 10 years, the authors reported that the risk of endocrine or severe exocrine insufficiency in type 2 AIP patients treated with glucocorticoids was low (5% and 25% respectively), a lower extent compared to type 1 AIP [15]. Notably, in line with the existing literature, none of the patients developed pancreatic adenocarcinoma during the observation period [15, 22]. Finally, the relapse rate was low (13%) and did not increase beyond 5 years. All together, this important long-term study provides evidence that type 2 AIP has overall a more benign clinical outcome than type 1 AIP and suggests termination of a pancreas-specific follow-up surveillance beyond 5 years due to negligible relapse and PDAC risk. Importantly, gastrointestinal follow-up remains of utmost importance to screen for IBD.

The length and timing of follow-up in type 1 AIP patients is still a matter of debate, but lifelong follow-up is suggested due to the increased rate of IPMN and PDAC reported in retrospective studies [58, 88]. Indeed, Keller–Sarmiento et al. unveiled a higher prevalence of cancers in IgG4-RD patients compared with matched controls. Notably, most cancers developed within 3 years of IgG4-RD diagnosis, advising a tight surveillance in this time frame [89].

In conclusion, a rapid rate of knowledge acquisition has marked the last decades of research in AIP with regard to pathophysiology, diagnosis, and mechanistic therapies. With the increased awareness of this condition, this knowledge acquisition will only continue to grow and benefit patients by providing novel insights into important questions related to human immunology.

Author Contributions

All the authors equally contributed.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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