SMART Approach

Treatment Updates for Type 1 Autoimmune Pancreatitis (AIP) and IgG4-Related Diseases

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1. Overview

Autoimmune pancreatitis (AIP) is a chronic inflammatory disease of the pancreas that is distinguished by unique pathogenic mechanisms and treatment considerations. Three subtypes of AIP are recognized, with Type 1 (the pancreatic manifestation of IgG4-related disease) being much more common than Type 2 or Type 3. Previously, we published a detailed review of AIP that provides an overview of these subtypes, diagnostic approaches and treatment considerations. Here we provide important updates on new B cell-targeting therapies including inebilizumab and obexelimab, and other novel therapies including efgartigimod and other agents in ongoing clinical trials.

2. Background

Type I AIP is the pancreatic manifestation of IgG4-RD, a fibroinflammatory disease often manifesting with multiorgan tumor-like masses or diffuse organ enlargement. [(1)] Early detection and diagnosis can be challenging, and 60-80% of patients present with irreversible organ damage. The pancreas is particularly susceptible to damage from IgG4-RD, which may take the form of new onset diabetes mellitus (DM), weight loss, and/or exocrine pancreatic insufficiency.

a. Diagnosis.

Diagnosis of Type 1 AIP typically follows the HISORt Criteria[(2)] that requires a combination of characteristic **H**istologic/ immunostaining on pancreatic biopsy (not fine needle aspiration), **I**maging, **S**erology, **O**ther organ involvement and **R**esponse to steroid **t**reatment. [(3)] The three classic histopathological features of type 1 AIP include: 1) a dense lymphoplasmacytic infiltrate, 2) fibrosis in a storiform, or whorling, pattern, and 3) obliterative phlebitis (best appreciated by a dedicated elastin stain). In addition, immunostaining to count the number of IgG4 expressing plasma cells (>10/HPF), and ratio of IgG4 to total IgG expressing cells (>40%) greatly supports the diagnosis. It is important to recognize that the histopathology and immunostaining findings must be interpreted clinically as other pancreatic diseases can mimic these including pancreatic ductal adenocarcinoma (PDAC). No single finding alone can confirm the diagnosis of IgG4-RD and caution must be applied to not misdiagnose patients based on histopathology alone.

Endoscopic ultrasound (EUS) guided fine needle biopsy (FNB) with a 22-gauge needle is an approach that yields adequate specimens in nearly three-quarters of cases, though multiple needle sizes are effective in achieving a diagnosis and ruling out pancreatic malignancy. In contrast, EUS fine needle aspiration (FNA) is not sufficient

Abbreviations: ACR, American College of Rheumatology; ADCC, antibody-dependent cellular cytotoxicity; AIP, autoimmune pancreatitis; BCMA, B-cell maturation antigen; BLA, biologics license application; BMP, basic metabolic panel; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CBC, complete blood count; CD4+ CTLs, CD4-positive cytotoxic T lymphocytes; CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; EUS, endoscopic ultrasound; FcRn, neonatal Fc receptor; FNA, fine-needle aspiration; FNB, fine-needle biopsy; gMG, generalized myasthenia gravis; HISORt, Histology, Imaging, Serology, Other organ involvement, Response to therapy; HPF, high-power field; HR, hazard ratio; IFN-γ, interferon gamma; IgG4-RD, immunoglobulin G4–related disease; IL, interleukin; INEB, inebilizumab; ITP, immune thrombocytopenia; IV, intravenous; LFT, liver function tests; mAb, monoclonal antibody; NCT, National Clinical Trial (ClinicalTrials.gov identifier); PDAC, pancreatic ductal (continued) adenocarcinoma; PDGF-B, platelet-derived growth factor B; PSC, primary sclerosing cholangitis; RTX, rituximab; TEAE, treatment-emergent adverse event; TGF-β, transforming growth factor beta; WInS, Withdrawal of Immunosuppressants and Steroid in stable IgG4-RD.

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for diagnosis as these specimens lack tissue architecture and important differential diagnoses including PDAC, primary sclerosing cholangitis (PSC), cholangiocarcinoma, and celiac disease are all capable of driving an IgG4-expressing plasma cell infiltrate. [4, 5]

Biopsy of the pancreas requires expert approaches as obtaining adequate core biopsies is essential and biopsy carries the risk of triggering acute pancreatitis. In practice, pancreatic biopsy is generally reserved to rule out a pancreatic malignancy in the setting of a pancreatic mass. Biopsy is not needed for diagnosis when other diagnostic features are present such as: radiologic features of a hypoattenuating rim enveloping the pancreas, diffuse, sausage-shaped enlargement of the pancreas, or when there are extra-pancreatic manifestations of IgG4-RD particularly including multifocal biliary strictures.[6]. A dramatic response to glucocorticoid treatment can also be compelling evidence for Type 1 AIP and against pancreatic malignancy. If only the pancreas is involved, other causes of pancreatitis must be ruled out, including type 2 AIP. In contrast, biopsies are needed if imaging reveals a mass-forming/focal lesion where pancreatic adenocarcinoma remains in the differential diagnosis.

b. IgG4-Related Disease

IgG4-RD affects a wide variety of organs. These commonly include the pancreas, lacrimal glands, major salivary glands and the retroperitoneum (typically in a pattern that is anterolateral or circumferential to the infrarenal abdominal aorta). The orbits, lungs, bile ducts, lymph nodes, prostate, coronary arteries, aorta, and kidneys can be affected in a smaller portion of patients while many rare manifestations also exist including the thyroid gland, pachymeninges, pituitary gland, skin, liver, and gallbladder. Among the many potential manifestations of IgG4-RD, type 1 AIP is most strongly associated with biliary involvement with a frequency of 25-50% across various reports[3, 7, 8] and this pancreatobiliary presentation represents a distinct organ-based cluster of patients with IgG4-RD. [9]

Because of the involvement of multiple organs, AIP is best managed by a multidisciplinary team approach that includes a pancreatologist, rheumatologist, and potentially, other specialists depending on extra-pancreatic organ involvement.

3. Treatment considerations

The mainstay of remission induction treatment for type 1 AIP (and multiorgan IgG4-RD) has been high-dose oral glucocorticoids with a gradual taper to discontinuation over 2-3 months. We typically use prednisone at 40 mg per day for 4 weeks with a slow taper of 5 mg per week for a total of 12 weeks of therapy with alternative dosing schedule of 40 mg daily for 4 weeks, then 20 mg per day for 2 weeks, 10 mg per day for 2 weeks, and lastly 5 mg per day for 2 weeks.[6] While extremely effective at achieving remission, approximately 60% of patients treated with glucocorticoid monotherapy relapse within 9 months of completing the course.[10, 11] Risk factors for relapse include an elevated serum IgG4 level, elevated serum IgE level, the presence of peripheral eosinophilia, and multiorgan involvement. Moreover, IgG4-RD commonly causes irreversible organ damage and therefore, the prevention of additional disease relapses may be as important as initial remission induction therapy. Thus, the risk for future relapses and assessment of organ damage after successful remission induction, as well as the tolerability of additional prolonged glucocorticoid courses are all important considerations in defining a treatment plan for each patient. Fortunately, steroid-sparing therapies are available, and others are on the horizon, which provide important treatment options.

a. Considerations in selecting therapy

While steroids may be initially effective, they have numerous adverse effects and drawbacks that limit their utility, particularly for long-term maintenance treatment. We consider four domains in selecting an optimal therapeutic approach for our patients with type 1 AIP.

Patient Characteristics
- Age
- Comorbidities
- Preferences
- Cost
- Practice Patterns

Efficacy
- Induction
- Maintenance
- Relapse Rate

Disease Characteristics
- Multiorgan involvement
- History of relapse
- Risk factor for relapse

Safety
- Infectious complications
- Long-term complications
  (e.g. osteoporosis, diabetes mellitus, liver toxicity, myelosuppression)
- Infusion reactions

b. Categories of Treatments.

Steroid-sparing agents are important considerations in treating IgG4-RD because of the relapse rate associated with glucocorticoid monotherapy for remission induction

and the long-term toxicities associated with glucocorticoids for maintenance of remission. Steroid-sparing agents include conventional immunosuppressive medications (e.g. mycophenolate mofetil, azathioprine, etc.) and B-cell directed therapies, which can be used both as adjunctive therapy to glucocorticoids to induce more durable remission and as maintenance treatment to prevent relapse.

Conventional Immunosuppressive Medications

Conventional immunosuppressive medications including azathioprine, mycophenolate mofetil, 6-mercaptopurine, methotrexate, cyclophosphamide, leflunomide, iguratimod, and thalidomide have all been studied in the context of IgG4-RD. The addition of some conventional immunosuppressive medications to glucocorticoids including mycophenolate, cyclophosphamide, and iguratimod [12-14] has been shown to induce more durable remission of IgG4-RD than glucocorticoid monotherapy. While multiple studies have suggested a steroid-sparing effect of conventional immunosuppressive medications, they have been methodologically limited including small observational, open-label studies, and randomized trials without double blinding or placebo control. The role of conventional immunosuppressive agents for maintenance of remission is supported by the Withdrawal of Immunosuppressants and Steroid in stable IgG4-RD (WInS) trial[15], which was a randomized, open-label study including 146 patients, which demonstrated a significantly lower likelihood of disease relapse with continuation of the conventional immunosuppressive medication versus withdrawal. However, given the limitations in the methodology used to study these agents relative to B-cell targeted therapies, conventional immunosuppressive medications are mostly used if B-cell targeted therapies are inaccessible or not tolerated.

c. B-cell Directed Therapies

While both B and T cells are considered central to the pathology of IgG4-RD, only B cells have proven to be pathogenic through the rapid and consistent reduction in disease activity with B cell depleting agents.[1] B cells differentiate into plasmablasts and plasma cells in a T cell-dependent manner, relying on cytokines such as IL4, IL10, and IL21. These cells recognize self-antigens [16] and show evidence of oligoclonal expansion [17, 18] in the peripheral blood and lesional tissues of IgG4-RD. Although B cells and plasma cells are abundant in IgG4-RD lesions and IgG4 class-switching is such a prominent feature of this disease, the primary pathogenic function of B cells in IgG4-RD is thought to be that of antigen presentation to tissue-damaging T cells such as cytotoxic $CD4^+$ T lymphocytes ($CD4^+$ CTLs). In fact, the reduction of circulating $CD4^+$ CTLs following B cell directed therapies has been demonstrated with both B cell depleting and B cell inhibiting therapies. [19-21] Cytotoxic T cells cause tissue damage through direct cytotoxicity (releasing perforin, granzyme A/B, granulysin, etc) and fibrosis-driving cytokines (INF-γ, IL-1β, TGF-β etc.).[22] B cells further promote fibrosis through production of pro-fibrotic mediators (e.g., PDGF-B) and enzymes involved in organization of the extracellular matrix.[23] This process can be halted in multiple ways including the depletion or inhibition of B cells

d. Rituximab

Rituximab, a chimeric (mouse–human) anti-CD20 directed B cell depleting monoclonal antibody (mAb) was the first B cell-targeting drug studied in the context of IgG4-RD and type 1 AIP.[24, 25] It mediates B cell death through both antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity. These processes rapidly clear circulating B cells within days of administration, while tissue-level depletion of B cells is only partial.[26] CD20 is a transmembrane protein expressed on cells of the B lineage from the pre-B cell stage to memory B cells, but is downregulated by plasmablasts and plasma cells. Thus, rituximab likely works in IgG4-RD by depleting important antigen presenting cells that are essential to sustaining the tissue-destructive, pathogenic T cell response.

To induce remission of IgG4-RD, rituximab is typically given in conjunction with glucocorticoids while literature to support the use of rituximab as monotherapy without any glucocorticoids is limited. We typically dose rituximab as two infusions of 1,000 mg each spaced two weeks apart. Single 1,000 mg infusions can be administered every 6 months as a fixed maintenance regimen, or used "on demand" if the disease begins to relapse. Observational series and meta-analyses report high rates of complete or partial remission (approximately 70–90 %) and reduced relapse risk, although re-treatment is often required after B-cell reconstitution.[27] In one study comparing rituximab remission with rituximab maintenance, 86% of patients achieved remission. [28] The 3-year event relapse rate was 45% in the induction arm and 11% in the maintenance arm with a median duration for relapse of 15 months. [28] Importantly, while effective at achieving remission, the risk of infection in this trial was 14%. Although rituximab is highly effective at treating IgG4-RD, without a randomized, double-blind, placebo-controlled trial having been done, its use remains off-label without approval from regulatory agencies. Based on these data, maintenance therapy is preferred. If a fixed dosing regimen is used for maintenance, eventually spacing out treatment intervals is favored if disease activity appears controlled to avoid risks of long-term serial exposure including infection and

hypogammaglobulinemia which have been well described in RTX therapy.

4. New B-Cell Directed Therapies

Over the past two years, two randomized, double-blind, placebo-controlled trials have been completed in IgG4-RD leading to the first FDA-approved therapy for this disease, with an additional medication likely to be approved in the near future.

FDA approved or pending drugs.

B-cell Depletion

a. Inebilizumab *(Uplizna)*

Inebilizumab (INEB) is a humanized anti-CD19 monoclonal antibody that depletes a broader range of B-lineage cells (including $CD20^-$ plasmablasts) than rituximab. The Fc-portion of INEB is also engineered (i.e. afucosylated) for enhanced ADCC. While this may hold promise for more effective tissue-level depletion of B cells, it also permits a much lower dose (300 mg) relative to rituximab equating to far shorter infusion times. On 3 April 2025, the FDA approved INEB as the first and only therapy specifically indicated for adult IgG4-RD. Approval was based on the phase 3 MITIGATE trial (NCT04540497), a randomized, double-blind, placebo-controlled study of 135 patients with active IgG4-RD.[11] Inclusion criteria were adult patients diagnosed with IgG4-RD, satisfaction of the 2019 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria, recent IgG4-RD flare requiring treatment escalation, and the involvement of at least two organ systems.

INEB (300 mg IV on days 1 and 15, then week 26) reduced the risk of treated, adjudicated flares by 87 % versus placebo (HR 0.13; 10 % vs 60 % of patients experienced ≥1 flare) and increased rates of flare-free, glucocorticoid-free complete remission at week 52. Both B-cell and IgG4 levels decreased significantly in the treatment group. The most frequent adverse events included urinary-tract infection and lymphopenia; the overall safety profile was consistent with prior reports of B cell depletion. The maintenance dosing employed in the trial was one infusion every 6 months after the induction course. At the 2026 EULAR Annual meeting, the open-label period data for the MITIGATE trial was presented. Key findings demonstrated that of the 56 patients in the INEB group who remained on treatment, 0% of patients had flares and among the patients in the placebo group who crossed over into the INEB group, only 5.9% had a flare, which occurred in the first few weeks of the open-label period. (EULAR Abstract Archive: Stone, JH Volume 85, supplement 1, year 2026, page s646)

B-cell inhibition

a. Obexelimab

Obexelimab is a bifunctional mAb that binds to CD19 on the surface of B cells (thereby interfering with the functional role of CD19 in B cell survival, differentiation, and activation) while the Fc-domain is engineered with enhanced binding affinity to the inhibitory Fc receptor, FcγRIIb. FcγRIIb is the only inhibitory Fc receptor and the only Fc receptor type expressed by B cells. Ligation of FcγRIIb on B cells suppresses B-cell activation by interfering with signals downstream of the B-cell receptor *without* direct B-cell depletion.[29] While there is an approximate 50% reduction in circulating B cell numbers while on treatment with obexelimab, this is thought to be due to sequestration of B cells in lymph nodes and it is considered to be a B-cell inhibitor rather than a depleting agent. In the phase 3 INDIGO trial (NCT05662241; 194 patients)[30], weekly subcutaneous obexelimab (250 mg) resulted in a 56% reduction in flares requiring rescue therapy (HR 0.44; 27% vs 55 % of patients flared) and improved complete-remission rates while markedly reducing cumulative glucocorticoid exposure (37.1% versus 19.6%, P = 0.005). Cumulative glucocorticoid use was also reduced in the treatment group from 929.8 mg in the placebo group compared to 329.5 mg in the Obexelimab.[30] Adverse events were generally comparable to placebo (arthralgia, hypersensitivity, diarrhea more frequent with drug; serious adverse events were fewer in the obexelimab group compared to placebo [10.3% versus 18.6%].

Based on the results of the INDIGO trial, a biologics license application was submitted to the FDA (May 2026). FDA approval is pending administrative review (August 2026).

Phase 3/Ongoing

Bruton's Tyrosine Kinase Inhibitors

Bruton's tyrosine kinase (BTK) is a key mediator of B-cell receptor signaling and plays an essential role in the maturation, activation, function, and differentiation of B cells and their subsequent production of antibodies.[31] Two oral agents, rilzabrutinib and zanubrutinib have now completed Phase II trials in IgG4-RD. in Phase III trial, RILIEF, **NCT07190196.**

a. ***Rilzabrutinib****:*

In the phase 2, open-label trial of rilzabrutinib in IgG4-RD (**NCT04520451)**, 27 patients were enrolled, with 9 having pancreatic involvement. There were two cohorts with 13 and 14 patients enrolled, respectively. At the end of the trial, 70% of patients were in remission and steroid free and had an improvement in the IgG4-responder index of ~

11 points. Serious treatment-emergent adverse events (TEAEs) occurred in 2 participants, 1 resulting in death, but both events were judged unrelated to the study drug. The most frequent TEAEs were diarrhea, 40.7% (11/27); coronavirus disease 2019, 18.5% (5/27); and dizziness, 18.5% (5/27).[32]. A phase III trial, RILIEF (**NCT0719196**) is now underway.

b. Zanubrutinib:

In the phase 2, open-label, trial of zanubrutinib in IgG4-RD, 10 patients with lacrimal and submandibular gland were enrolled and treated with zanubrutinib 80 mg twice daily for up to 24 weeks without concurrent glucocorticoid treatment. [19] At week 24, lacrimal gland size reduced by a mean of 47% and submandibular glands by 30%, demonstrating the efficacy of BTK inhibition as monotherapy for IgG4-RD. IgG4-RD Responder Index declined alongside reductions in serum IgG4 and circulating plasmablasts. The treatment was well tolerated.

Early phase human studies.

a. ***Efgartigimod*** (Vyvgart)

Efgartigimod is a neonatal Fc-receptor (FcRn) antagonist that accelerates IgG catabolism, thereby lowering circulating IgG without depleting B cells. The FcRn is a developmentally regulated, major histocompatibility complex class I related molecule that binds to the FC region of all IgGs and to albumin in a pH-dependent manner.[33] Binding of FcRn to IgG and albumin protect them from destruction resulting in prolonged half-lives for these circulating proteins. Blocking FcRn allows for more rapid clearance of IgGs.

FcRn transports IgG across polarized cells and is important for IgG movement across barrier surfaces such as the placenta and gut enterocytes. It also plays a role in regulating cellular pathways of immunity associated with myeloid cells.[33] Thus, while blocking FcRn has potential therapeutic benefits for a wide variety of autoimmune and immune-mediated diseases[33], the benefits must be weighed with off-target risk such as infectious diseases and cancer control.

Efgartigimod has been approved for treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) and generalized myasthenia gravis (gMG) in the United States and for immune thrombocytopenic purpura (ITP) in Japan. Efgartigimod is primarily used for gMG with four doses given once weekly by infusion or subcutaneously (Vyvgart Hytrulo).

Efgartigimod has been used off-label for IgG4-RDs. A phase 2a, single-site, open-label study (NCT07025330; Stanford University) evaluating weekly subcutaneous efgartigimod in adults with IgG4-RD. The primary outcome is volumetric reduction of lacrimal/salivary glands or pancreas. It is active and closed for recruitment (target n ≈ 5; estimated completion 2028).

Anti-CD19 Chimeric Antigen Receptor T Cell Therapy

Keitel and colleagues[34] reported treatment of a 60 year-old man with IgG4-RD involving the pancreas, hepatobiliary tract, and lungs, who was refractory to long-term immunosuppression, including low-dose rituximab. He was treated with autologous CD19-directed chimeric antigen receptor (CAR) T cells through a German compassionate use program. Anti-CD19-CAR T cells were chosen with the goal of deeper tissue-level B cell depletion and carries the hope of "resetting" the B cell compartment such that naïve B cells that emerge after ablation will not be self-reactive to the same antigens that were driving IgG4-RD pre-treatment.

The patient developed grade 3 neutropenia (absolute neutrophil count <500/μl) and grade 2 anemia (hemoglobin 8–10 g/dl) within the first week after infusion. However, the clinical response was rapid and sustained, documented by improvements in imaging, organ function, and even normalization of the IgG4 level, which had not been achieved for over a decade with previous therapies, and patient-reported outcomes. No disease flares occurred during the 12-month follow-up period despite the discontinuation of all immunosuppressive therapy

Anti-BCMA CAR-T therapy

B-cell maturation antigen (BCMA) is highly expressed on plasmablasts and plasma cells. Anti-BCMA CAR-T cell therapies have been developed to target and deplete these cells. This approach has been successful in treating refractory multiple myeloma[35], and now has been tested, off-label, for IgG4-RD.

Two cases of refractory, multiorgan IgG4-RD were treated with anti-BCMA CAR-T cells after lymphodepletion with cyclophosphamide and fludarabine (Clinical Trials.gov: NCT06497387) Treatment resulted in rapid and deep reductions in serum IgG4/IgE, radiographic regression of lesions, and sustained drug-free complete remission lasting ≥9 months (now >17 months[36]) without severe cytokine-release syndrome or neurotoxicity.[37]

Additional CAR-T Studies.

Targeting B-cells and plasma cells has implications for treating a wide variety of cancers and autoimmune diseases. [38] Phase 1/2 investigator-initiated trials (including allogeneic and dual-targeting constructs) for IgG4-RD are ongoing. Multiple reports of these studies, including off-label (IRB approved) treatment of refractory

IgG4-RD with new agents, are expected within the next few years.

Although these early anti-CD19 and anti-BCMA CAR-T cell studies show promise in severe, refractory IgG4-RD cases, there are also significant downsides including lymphodepletion, infectious complications, cytokine release syndrome, neurotoxicity, and a substantial cost to the health system. [39] Time and further experience will tell which of these approaches is the best option for refractory disease and if such therapies are needed in the context of an expanding armamentarium of B cell directed options including inebilizumab, obexelimab, and potentially, BTK inhibitors.

Investigational / refractory only

γδ T-cell-Anti-CD20 antibody (ACE1831)

ACE1831 is an off-the-shelf allogeneic γδ T-cell product conjugated (via click chemistry) to anti-CD20 antibodies. A phase 1b/2a open-label, multicentre study (NCT07061938; Acepodia) evaluating safety, persistence, and efficacy (complete-remission rate at 24 weeks) in active IgG4-RD, with or without lymphodepletion, began enrolment in early 2026. Preclinical data support potent B-cell cytotoxicity with a potentially favorable safety profile relative to conventional autologous CAR-T.

These advances underscore the centrality of B-lineage cells in IgG4-RD and expand the therapeutic armamentarium beyond glucocorticoids and conventional B-cell depletion, offering the prospect of deeper, more durable, and steroid-sparing disease control.

5. How we do it.

1. **Diagnosis**: The diagnosis of IgG4-RD typically requires a combination of imaging, physical exam findings, serology, or biopsy. We recommend utilizing the ACR/EULAR Classification Criteria for IgG4-Related Disease or the HISORt criteria for AIP.

2. **Evaluation**: We recommend that all patients with suspected IgG4-RD undergo cross-sectional imaging of the chest, abdomen and pelvis and a thorough head and neck examination to identify all organs which are involved. In addition, patients should have serum IgG, IgE, IgG4, CBC with differential, LFT, BMP, ESR, CRP, and microalbumin/creatinine ratio checked to determine disease severity and risk of relapse.

3. **Initial treatment**: In our center, patients requiring prednisone therapy are managed by pancreatology or rheumatology. In patients that have multiorgan involvement or are high risk for relapse, patients are referred to rheumatology for initiation of B-cell therapy. Dosing schedule includes Prednisone 40 mg by mouth daily for 4 weeks, then taper by 5 mg per week for a total of 12 weeks.

4. **Initial pancreatic evaluation**: For patients where the diagnosis is not clear and a patient presents with a pancreatic mass or obstructive jaundice, we refer for endoscopic ultrasound for fine needle biopsy to rule out a pancreatic adenocarcinoma. A trial of steroids is generally given to confirm the diagnosis and then patients are transitioned to B-cell therapy once PDAC has been ruled out and the diagnosis of AIP has been confirmed.

5. **When is a case "refractory**"? When we consider a case refractory when non-glucocorticoid therapies are considered. An 8-12 week course of steroids can be considered in patients with mild, single organ disease or those with isolated swelling of the parotid or submandibular glands. However, if a patient relapses, has multiorgan disease, very elevated IgG4 or IgE levels, B-cell therapy is considered as first line therapy.

6. **Use of Rituximab, or other newer agents**: While steroids have been considered "first line", there are significant side effects including diabetes, osteopathy and infections associated with their use. We know that patients with multiorgan involvement, elevated serum IgG4 and IgE levels are at high risk for relapse. In patients that meet any of these criteria we will consider up front B-cell therapy. The specific IgG4 and IgE cut offs to suggest need for B-cell therapy are a source of ongoing investigation.

When dosing Rituximab, pretreatment is recommended. This includes: Methylprednisolone 100 mg IV once and diphenhydramine 50 mg po or IV once is given 30 minutes prior to each infusion to minimize the risk of infusion reactions.

Rituximab dosing is 1000 mg IV given over 4-6 hours, on day 1 and day 15.

In the Mitigate trial, Methylprednisolone 100 mg IV once, diphenhydramine 50 mg po once, and acetaminophen 500-650 mg po once was given 30 minutes prior to each infusion.

The Inebilizumab dose is 375 mg IV given on day 1 and day 15. Inebilizumab can be infused over 90 minutes.
Prior to B-cell depletion, patients need to be screened for Hepatitis B, Hepatitis C, HIV, and tuberculosis. B-cell depletion can reactivate Hepatitis B and lead to liver failure. Appropriate treatment with Tenofovir should be considered in a patient that is Hepatitis B positive. Appropriate vaccinations should be given prior to B-cell therapy. Key vaccinations include Shingles, COVID-19, Influenza, Measles (only if the patient is not immunosuppressed). The optimal timing is 2-4 weeks prior to initiation of B-cell therapy to allow for appropriate antibody generation.

7**. Clinical trials:** We carefully screen almost all of our patients for clinical trials.

8. **Other clinical pearls:** While B-cell therapy is effective, appropriate evaluation of infections such as HIV, Hepatitis C, Hepatitis B and Tuberculosis are required to prevent worsening or reactivation of these infections during treatment. Vaccinations should also be given prior to initiation of B-cell therapy or at the 6 month mark after receiving B-cell infusion to ensure patients can generate antibodies against various pathogens.

6. Conclusions.

In conclusion, AIP and IgG4-RD are rare diseases that may be challenging to diagnose. However, once the diagnosis is confirmed careful assessment of disease severity and risk of relapse should guide therapy rather than an initial course of steroids for all patients. This approach will help minimize steroid exposure and toxicity to patients and help ensure remission.

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