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Autoimmune pancreatitis

Optimising corticosteroid treatment for autoimmune pancreatitis

Amaar Ghazale, Suresh T Chari

Unanswered questions

Autoimmune pancreatitis (AIP) is part of a systemic fibro-inflammatory disease that can involve multiple organs which characteristically have a lymphoplasmacytic infiltrate rich in IgG4-positive cells. IgG4-related systemic disease (ISD) has been proposed by Kamisawa *et al* as the umbrella term to describe this multi-organ disease.¹ Although the fibrosis in ISD can often lead to damage and even destruction of the involved organ, the inflammatory process typically responds to steroid treatment. However, the resolution of the inflammatory process in ISD may occur spontaneously without steroid treatment, especially in AIP.^{2,3} The effect of steroid treatment on the natural history of AIP is not known as it is only recently that large series of AIP are being reported.

In this issue of *Gut* (page 1719), Hirano *et al*⁴ report the results of a retrospective review of 42 AIP patients of whom 19 were treated with steroids. The authors' goal was to determine the effect of steroids on subsequent disease relapse by comparing "unfavourable events" in steroid treated patients with those in historical controls presenting before 2003 who did not receive

steroids. "Unfavourable events" included the development of obstructive jaundice related to distal biliary stricture, sclerosing cholangitis with elevated liver enzymes, growing pancreatic pseudocyst or other extra pancreatic lesions that required treatment (retroperitoneal fibrosis, interstitial nephritis, sialoadenitis). "Unfavourable events" were less in the steroid treated group compared to controls (32% vs 70%, $p = 0.01$). The authors conclude that steroid treatment could reduce subsequent disease relapse and thus recommend the early introduction of steroids.

DEFINITIONS OF TREATMENT OUTCOMES

When discussing treatment in AIP, it is important to use specific terms that help identify treatment goals and responses. Remission refers to the resolution of disease-related symptoms and radiological abnormalities, whether spontaneously (spontaneous remission) or with steroids (steroid-induced remission), keeping in mind that in AIP, fibrosis-induced glandular and ductal distortion may prevent complete restitution of gland to normal

architecture (and hence normal appearance on imaging). Induction of remission refers to the treatment of acute symptomatic and radiological manifestations of AIP with the goal of achieving disease remission. Maintenance treatment involves the use of immunosuppressive therapy to prevent disease relapse and maintain remission. Disease relapse is the recurrence of radiological manifestations of AIP (with or without symptoms) in the pancreas or extra pancreatic-involved organs. In the Hirano study,⁴ most patients in the steroid group received long-term maintenance steroid treatment after initial disease remission. There are two questions that need to be addressed regarding steroid treatment in AIP: (1) what is the role of steroids in inducing disease remission at initial presentation and (2) is there a need for maintenance treatment to maintain remission and, if so, what is the most appropriate treatment?

MANAGEMENT OF THE ACUTE PRESENTATION OF AIP

Our understanding of the effects of steroid treatment in the acute phase of AIP is evolving. It appears that although spontaneous remissions do occur in AIP, the use of steroids brings about remission consistently and quicker than if no treatment were given. Steroids relieve disease-related symptoms (abdominal pain, obstructive jaundice) in most patients.³ Concomitant with amelioration of symptoms, an improvement in radiological abnormalities is also seen with treatment. If there is any doubt about the diagnosis, the rapid response to steroids is reassuring and confirms the diagnosis. This includes resolution of pancreatic changes

(ductal abnormalities, enlargement or mass) and of extra pancreatic manifestations (biliary strictures, retroperitoneal fibrosis, and so forth). However, since AIP is associated with intense fibrosis, many radiological changes (for example, ductal changes, retroperitoneal fibrosis) may improve only partially or in some cases remain unchanged after treatment. We think steroids should be offered to all AIP patients with active disease. There appears to be no role for steroids in patients who present in the post-acute phase with pancreatic atrophy unless they have extra pancreatic disease requiring treatment.

There is no consensus to date on steroid regimen and duration of treatment in AIP. Starting doses range from 30–40 mg in most studies.^{2 3 5 6} In the current study, starting doses used were 30–50 mg daily.⁴ These doses are effective in the majority of patients; however, it is not known whether lower doses (10–20 mg) would also be effective. Starting doses are typically given for 3–4 weeks followed by a taper of varying duration. We have used prednisone 40 mg daily for 4 weeks followed by taper of 5 mg per week (total of 11 weeks of treatment).² Response is typically rapid with significant radiological improvement at 2–3 weeks.⁷ In patients who experience a complete radiological response, normalisation of imaging findings typically occurs at 4–6 weeks.⁷ Our most commonly used follow-up protocol involves repeat laboratory tests and imaging 4–6 weeks after commencing steroid treatment. If a biliary stent was placed on presentation for biliary strictures, stent removal is possible 6–8 weeks after starting steroids in the majority of patients (unpublished data).

DISEASE RELAPSE IN AIP

In the study by Hirano *et al*,⁴ the authors compared the outcomes of conservative treatment in historical controls with the outcomes of treatment with steroids in the current era. Based on a higher rate of “unfavourable events” in the conservative group, the authors conclude that steroid treatment could reduce subsequent disease relapse. Two factors make it hard to come to this conclusion based on data presented. First, the control and treatment arms in this retrospective study are not comparable; sclerosing cholangitis was not seen in any of the 23 conservatively managed patients, whereas 6/19 (32%) steroid treated patients had sclerosing cholangitis, the latter figure being closer to that reported by others. This suggests sclerosing cholangitis was under recognised at presentation in the historical controls and may have subsequently presented as an “unfavourable event”.

Second, steroid patients were very often indefinitely left on maintenance steroids. Because of these reasons it is not entirely clear from this study that treatment of the initial presentation with brief course of steroids prevents future relapses. However, results of other studies do confirm that relapses after steroid treatment or while steroids are being tapered are common in AIP: approaching 20–40%.^{8–10} It appears that recurrence of biliary strictures may be more common than recurrent pancreatic disease (as suggested in the Hirano study⁴ and based on unpublished data from our centre).

To identify relapses early, periodic follow up of patients who have initially responded to treatment is recommended. In the study by Hirano *et al*,⁴ imaging was performed every 6 months with laboratory testing every 3–6 months to assess for relapse. Our follow-up protocol is largely based on the organ involved. In patients with biliary strictures, it has been our practice to repeat laboratory testing (liver enzymes, serum IgG4) every 12 weeks for the first 1–2 years. In patients without biliary disease, assessment for recurrence is more difficult and we have monitored patients for recurrent symptoms and only then do we consider imaging. These practices will likely be refined as more data on long-term outcomes become available.

TREATMENT OF DISEASE RELAPSE

The high frequency of disease relapse has lead many Japanese investigators to maintain patients on low dose daily prednisone (2.5–10 mg) over the long term³ as was done in the current study.⁴ The study by Hirano *et al*⁴ answers an important question: can chronic immunosuppressive treatment with steroids prevent relapses in the pancreas and other organs? There was a significantly lower relapse rate in the steroid treated group compared to untreated patients (32% vs 70%, $p = 0.01$).⁴ Yet the relapse rate in the steroid group remained high (32%) despite maintenance steroids.⁴ Other Japanese studies have found relapse rates on low-dose steroids ranging 5–30%.^{11 12}

Instead of using long-term low-dose steroids we have opted to use immunomodulatory medications for maintenance of remission in patients who relapse after steroid withdrawal. In our experience, azathioprine (2 mg/kg daily) or mycophenolate mofetil (750 mg twice daily) appear to be equally effective in maintaining remission (100%, median follow up 6 months) after relapse in a small number ($n = 7$) of patients (unpublished data). Identification of risk factors for relapse may help us determine the high-risk patients who would benefit from

maintenance treatment upfront, and allow short term treatment in lower risk patients who may not need long-term treatment. Furthermore, although our preliminary data suggests a benefit of long term treatment, this needs confirmation in larger studies.

The choice of maintenance treatment (low-dose steroids versus immunomodulatory drugs) has not been studied. AIP patients are typically elderly patients and are at high risk of developing steroid-related complications (osteoporosis, diabetes, cataracts, and so forth) as some patients in the Hirano study did (one vertebral fracture, one osteonecrosis of femoral head, two diabetes requiring discontinuation of treatment). Studies of low-dose steroids in rheumatological diseases suggest that doses less than 7.5 mg daily have fewer side effects than higher doses;¹³ however, this remains controversial. Mean patient age in these studies was also younger than typically seen in AIP. Furthermore, in the Hirano study⁴ (and others), relapse rates remain high (~ 30%) despite use of low-dose maintenance steroids.

Data on immunomodulatory drugs in AIP is lacking. We have had success in a small number of patients with no serious side effects. Others have also anecdotally reported cases as well.¹⁴ Similar to steroids, immunomodulatory drugs have significant side effects. Azathioprine can result in allergic reactions, nausea, bone marrow suppression (2–5%), hepatotoxicity (2%), increased risk of infections and, rarely, pancreatitis.¹⁵ Significant side effects leading to drug discontinuation occur in approximately 10–30% of patients.¹⁵ Mycophenolate mofetil also has significant adverse effects, including headache (30–50%), diarrhoea (up to 30%), peripheral oedema (20%), hypertension, leucopenia and increased risk of infection.¹⁶ Both drugs also appear to have a slightly increased long-term risk of lymphoma.¹⁶ Thus the choice of long term treatment for maintenance of remission needs further studies with larger numbers of patients to assess the risk/benefit ratio of each approach. The duration of use of maintenance treatment is also unknown and needs further study.

UNANSWERED QUESTIONS

- Do steroids alter natural history? The Hirano study⁴ showed a lower incidence of relapse in steroid treated patients when maintained on low dose prednisone. It remains unclear if patients treated with short courses of steroids without maintenance treatment have lower relapse rates than untreated patients. If this were so, it may justify treating asymptomatic patients with

short courses of steroids to prevent long-term disease complications.

- Does treatment prevent the development of organ dysfunction? It appears that progression to pancreatic atrophy occurs in 30–50% of AIP patients. We have seen progression to cirrhosis in patients with biliary disease. It is unclear whether steroid treatment prevents or decreases the likelihood of disease progression.
- Do different manifestations of IgG4-related systemic disease have different disease courses? IgG4-related systemic disease can involve multiple organs (pancreas, bile duct, retroperitoneum, kidneys, lungs, salivary glands). It is unclear if relapse rates and long-term prognosis differ with various manifestations of the disease. If so, then mode and duration of treatment may need to be tailored based on the involved organ.
- What is the significance of isolated serological relapse? Serological relapse is a common clinical scenario. Patients present with elevated IgG4 after treatment but no recurrent disease on imaging. The significance of this finding and whether these patients eventually progress to clinical relapse is unknown. If so, then this would

support the early treatment of serological relapses.

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Chronic hepatitis C

Ursodeoxycholic acid in chronic hepatitis C

Raoul Poupon, Lawrence Serfaty

Cytoprotective but anti-apoptotic

The history of ursodeoxycholic acid (UDCA) therapy has been provided by Makino and Tanaka.¹ Identified in 1902 from polar bear bile by Hammarsten, UDCA was isolated and crystallised by Shoda in 1927. In 1936, its chemical structure was determined by Iwasaki at Okoyama Medical University. Several years later (1954) a chemist at Tokyo Institute of Technology, Kanazawa, described a method of synthesising UDCA from cholic acid and chenodeoxycholic acid. Three years later, Tokyo Tanabe Pharmaceutical Company launched “Urso” as a choleretic that could improve symptoms related to liver dysfunction and maldigestion. In 1961, Ishida, reporting his experience of Urso administration in chronic hepatitis, noted an improvement

of liver function tests in patients receiving the bile acid. This observation was replicated several times during the following two decades in Japan. Actually, UDCA really drew the attention of the western scientific community when it was shown that it could promote dissolution of cholesterol gallstones as well as chenodeoxycholic acid. The proof of concept study of UDCA in primary biliary cirrhosis showing a marked improvement in cholestasis under UDCA therapy was a further impetus for many studies aimed to define the biological properties of this “very special” bile acid. The putative mechanisms of action of UDCA in cholestatic disorders included at least, in part, stimulation of hepato-biliary secretion through apical insertion of transporter proteins, as

well as their up-regulation and activation, immunomodulation and protection against cytokines and hydrophobic bile acid-induced apoptosis.

In this issue of *Gut* (page 1747), Omata *et al*² have confirmed in a large-scale randomised study that a 24-week course of UDCA in patients with chronic hepatitis C was able to decrease significantly serum liver enzymes despite no effect on viral load. As cholestasis is not a common feature of chronic hepatitis, the mechanism involved in the aminotransferase lowering effect of UDCA is likely related to its anti-apoptotic property rather than an antagonising effect towards toxic bile acids at a biophysical level. Several mechanisms have been shown to operate in the UDCA anti-apoptotic function. In addition to an effect at the mitochondrial level, UDCA inhibits c-jun N-terminal protein kinase-dependent Fas trafficking to the plasma membrane and activates survival signals such as the epidermal growth factor receptor and the mitogen-activated protein kinase (MAPK). In addition, UDCA inhibits endoplasmic reticulum stress-mediated apoptosis.³

Omata *et al*'s paper raises two main issues: what is the relevance of transaminase normalisation in terms of disease progression in chronic hepatitis C and