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EDITORIAL

Current Concepts in the Treatment of Autoimmune Pancreatitis

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Summary

Autoimmune pancreatitis is a recently described chronic inflammatory disease of the pancreas which appears to be part of a systemic disorder characterized by a lymphoplasmacytic infiltrate in affected organs that is rich in IgG4 positive cells. The inflammatory component of the disease appears to resolve with steroid treatment, though relapses do occur. Here we briefly discuss the role of steroid therapy in the management of autoimmune pancreatitis.

Definition of Autoimmune Pancreatitis (AIP)

As recently defined by Chari *et al.* [1] "Autoimmune pancreatitis is a systemic fibro-inflammatory disease which afflicts not only the pancreas but also a variety of other organs including bile duct, salivary glands, the retroperitoneum and lymph nodes. Organs affected by AIP have a lymphoplasmacytic infiltrate rich in IgG4 positive cells and the inflammatory process responds to steroid therapy."

Steroid Responsiveness

Unlike usual chronic pancreatitis, AIP "responds" to steroid therapy. There are numerous reports of dramatic response of AIP to steroid therapy [2, 3, 4, 5, 6]. However spontaneous resolution without treatment has also been noted [1, 4]. As stated in its definition, AIP is a fibro-inflammatory disease. Intense inflammation is often accompanied by intense fibrosis. It is the inflammatory component that responds to steroid therapy; the fibrosis often permanently disfigures, damages and sometimes destroys the organ. While sometimes structural normalcy appears to be restored following steroid therapy, what is often seen is glandular atrophy with or without pancreatic insufficiency [4].

What Do Steroids Accomplish?

a) *Confirm the Diagnosis of AIP.* The clinical and radiological features of AIP can closely mimic those of pancreaticobiliary malignancy. There is therefore anxiety and trepidation about the possibility of malignancy, especially in those presenting with pancreatic mass or obstructive jaundice. Whilst the diagnosis of AIP is most secure in those with unequivocal histological changes and those with classic radiological and serological changes [1], a rapid and dramatic reduction in size of gland is also reassuring and confirms the correctness of the diagnosis [1]. However, a note of caution needs to be sounded regarding use of steroid therapy purely as a diagnostic test for AIP. It should be used only in those with a reasonably high suspicion of AIP (see [1]) and should never be used as a substitute for a thorough search

for etiology. It should be given only to patients with negative work up for known etiologies for pancreatic/biliary disease, especially cancer. Moreover, steroids should preferably not be given to those in whom response cannot be objectively assessed, for example, those without structural changes on imaging studies (pancreatic mass or enlargement or biliary strictures).

b) *Relieve Symptoms.* Dyspeptic and cholestatic symptoms caused by AIP are rapidly relieved by steroids [4]. Biliary obstruction is relieved allowing removal of stents. While most patients get biliary stenting during the work-up of the jaundice, we have occasionally seen patients whose jaundice is relieved by steroid therapy alone without need for stenting. It is unclear if biliary obstruction can be treated with steroid therapy alone without need for stenting before steroids are given.

c) *Improve Structural Abnormalities.* Concomitant with improvement in symptoms, an improvement in radiological changes is also seen [4, 7], including resolution of pancreatic duct abnormalities and pancreatic mass or enlargement. However, as noted previously, AIP is associated with intense fibrosis and some patients may be left with permanent changes on imaging studies (e.g., atrophic gland, irregular pancreatic and bile ducts, and retroperitoneal fibrosis) that do not resolve with steroid therapy [4]. This needs to be kept in mind when assessing "response" to steroids.

d) *Improve Endocrine Function (Diabetes) in the Acute Phase***.** During the acute presentation a subset of patients develops new-onset diabetes. Studies have shown that the diabetes seen in the acute presentation improves with steroid therapy [8]. We have also observed this in patients undergoing spontaneous resolution of inflammatory process. In the later phases of the disease diabetes is often worsened by use of steroids and in some patients may require reduction in dosage or even discontinuation.

Indications for Treatment

a) *Pancreatic Presentation - Acute.* The most common acute presentation of AIP is with obstructive jaundice with focal or diffuse pancreatic enlargement. While spontaneous resolution of this acute pancreatic presentation may occur, steroid therapy clearly hastens the resolution and in many patients is necessary to bring about improvement in clinical symptoms and accompanying radiological and serological abnormalities.

b) *Pancreatic Manifestations - Late or Post Acute.* In many patients the acute presentation is managed by endoscopic biliary stenting or surgical biliary bypass which results in resolution of clinical symptoms. Such patients may continue to show radiological evidence of persistent pancreatic mass or enlargement and/or distal biliary strictures. If the distal biliary stents cannot be removed due to persistent, tight biliary strictures, steroid therapy will allow removal of stents. The role of steroids in treating other asymptomatic radiological abnormalities, apart from the assurance that it provides regarding the diagnosis, is unclear. Long term studies will be needed for this. There is clearly no role for steroids in patients with atrophic pancreas unless they have extra-pancreatic disease that needs therapy.

c) *Extra-Pancreatic Presentation.* Steroid therapy has also been used to treat extra-pancreatic manifestations of AIP, most commonly biliary strictures. When biliary strictures cause jaundice, steroids cause biochemical normalization of liver test abnormalities and radiological improvement in or resolution of the strictures. Less is known about the long term benefits of treating asymptomatic biliary strictures.

Steroid Regimen and Length of Treatment

There is no consensus on the steroid dose or duration of treatment. I personally use prednisone at 40 mg/day for 4 weeks and

tapering it thereafter by 5 mg/week for a total of 12 weeks of therapy. There is a 30-40% relapse rate following withdrawal of steroids. Such patients will need a second course of steroids and occasionally maintenance steroids [4, 7] or other immunosuppressive. The literature on this is limited.

Unanswered Questions

a) *Do Steroids Alter the Natural History of AIP?* It is unclear if untreated patients suffer more relapses than steroid-treated patients. If this were so, it would justify treatment of asymptomatic patients. It is unclear if long term risk of disease is affected by treatment.

b) *Do Steroids Preserve Organ Function?* Diabetes and steatorrhea can develop after AIP initially by acute inflammation and later due to destruction of the gland by fibrosis. It is unclear if treatment with steroids reduces the long term incidence of pancreatic exocrine and endocrine insufficiency.

c) *Is There a Role for Chronic Immunosuppressive Therapy to Prevent Relapses in the Pancreas or Other Organs?* Long term studies are needed to determine how often patients suffer relapses in the pancreas or other organs and if long term immunosuppression can prevent relapses.

Keywords Autoimmune Diseases; Pancreatitis; Steroids

Abbreviations AIP: autoimmune pancreatitis

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