REVIEW

Treatment and Relapse of Autoimmune Pancreatitis

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Autoimmune pancreatitis (AIP) is a peculiar type of chronic pancreatitis whose pathogenesis involves autoimmune mechanisms. The steroid responsiveness has a significant impact on the diagnosis of AIP because patients with AIP and pancreatic cancer share many clinical features. This review focuses on the treatment and relapse of AIP. The goal of AIP treatment is remission of symptoms, serology, radiologic changes, or histology, which also applies to relapse. Although it is generally agreed that steroids should be offered to AIP patients with active disease, there is no standardized steroid regimen for AIP and no consensus on the dose and duration of steroid induction and tapering schedule, and optimal duration and dose of maintenance therapy. Obtaining a consensus on the optimal treatment regimen is very important to reducing the relapse rate. In this review, we discuss the treatment regimens used in many centers. (*Gut and Liver* 2008;2:1-7)

Key Words: Autoimmune pancreatitis; Treatment; Relapse

INTRODUCTION

Autoimmune pancreatitis (AIP) is a peculiar type of chronic pancreatitis in which autoimmune mechanisms are involved in the pathogenesis.¹ From a clinical aspect, steroid responsiveness of AIP implies a significant impact because patients with AIP and pancreatic cancer share many clinical features.²

Thanks to Japanese investigators, the ability to diagnose AIP has significantly improved during the past decade. Much less is, however, known about the detail of how to treat AIP, once the diagnosis has been made. This review

is focused on the treatment and relapse of AIP. That is because some of the complexities involved in the "treatment" have a bearing on "relapse" in AIP. For example, making consensus on optimum steroid regimen could in turn lead to low relapse rate.

DEFINITION OF TREATMENT OUTCOMES

When discussing treatment in AIP, it is important to use specific terms that help to identify treatment goals and responses.³ Despite the increasing number of papers published in the literature, there is a lack of consensus about terminology related to treatment outcomes including remission and relapse. Reaching consensus on their definition will be important to make comparisons of treatment outcome possible between different centers.

1. Remission

Treatment goal of AIP is to achieve remission. Remission could refer to symptoms, serology, radiologic changes or histology.³ Complete remission refers to the resolution of disease-related symptoms, and serologic, radiologic and histologic abnormalities. Resolution of symptoms (symptomatic remission) is achieved quickly in AIP as the obstructive jaundice and the accompanying symptoms may resolve within 2-3 weeks.^{3,4} However, serologic remission (especially, in normalization of serum IgG4 level) and radiologic remission (resolution of pancreatic mass and/or ductal strictures) may take more time.³ Histologic remission is harder to confirm due to difficulties in performing a biopsy of the pancreas.⁵ In practice, therefore, the end point of treatment is often symptomatic remission along with radiologic remission.³ Making consensus on definition of remission is very im-

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portant since it has a relation to determining the end point of treatment.

In a recent report from the United Kingdom,⁶ clinical remission was assessed in terms of pre- and poststeroid symptoms, liver biochemistry and radiological appearances. Serum IgG4 level was not included in the serologic remission. In their study, all patients whose IgG4 levels had failed to return to normal during steroid treatment eventually relapsed. After steroid treatment, a persistently elevated serum IgG4 may be observed in patients without symptoms or radiologic evidence of disease activity.⁷ Whether this represents subclinical disease activity is unclear. The possibility that a persistently elevated serum IgG4 level during treatment may guide the use of further immunosuppression, requires further study.⁶ Some of the relapsed patients whose serum IgG4 did not become normalized on steroid treatment could be representing a flare-up of residual disease rather than a true relapse after complete remission.

2. Relapse

Just as for remission, relapse may be symptomatic, radiologic, serologic, or histologic.³ Symptomatic relapse is usually associated with radiologic and serologic relapses. However, serologic relapse (e.g., increased level of serum IgG4 concentration) alone may be observed in patients without symptoms or radiologic evidence of disease activity.³ The definition of relapse is not uniform among authors. The relapse rate may vary according to the definition applied. In practice, the relapse is generally defined as the recurrence of radiological manifestations of AIP (with or without symptoms) in the pancreas or extrapancreatic organs.³ When defining relapse, authors generally do not distinguish between relapse of the pancreas versus occurrence of the disease in another organ, either de novo or true relapse of previously treated disease in that organ.³

TREATMENT

Unlike usual chronic pancreatitis, AIP dramatically responds to steroid therapy.² Steroid therapy brings about improvement in clinical symptoms and accompanying radiological and serological abnormalities. In principle, the treatment modality of AIP can be classified into medical and surgical therapy. The role of resective surgery is not yet clarified, and it is usually done without preoperative suspicion for AIP. It might be curative by removing the inflammation completely in the so-called mass-forming AIP.⁸ However, we cannot exclude the possibility of involvement of the residual pancreas after surgery.⁹ Accord-

ing to the study by Weber *et al.*,¹⁰ relapse rate after pancreatectomy was 28% (8/29) and biliary stricture was the most common clinical manifestation. There is also a concern about pancreatic insufficiency in recurred AIP patients after partial pancreatectomy. Given the substantial rate of relapse after pancreatic resection and current concept of AIP as IgG4-related systemic disease,^{11,12} steroid should be considered as the first choice of therapy in AIP.

1. Indication of steroid therapy

Although the patients with AIP respond well to prednisolone, it remains unclear whether steroid therapy is indispensable for all patients with AIP.¹³ There are anecdotal reports of spontaneous remission in AIP patients.^{11,14} Although spontaneous remission could occur in some patients with AIP, the use of steroids may bring about remission consistently and more quickly than in cases without the treatment.^{13,15} The role of steroids in treating asymptomatic radiological abnormalities is unclear. It is not certain if untreated asymptomatic patients would suffer more relapses than steroid-treated asymptomatic patients. If so, it would justify treatment of asymptomatic patients. It is generally agreed that steroids should be offered to AIP patients with "active" disease.¹⁵ The clinical manifestations of the patients with most evidence of active disease are obstructive jaundice due to stenosis of bile duct or the presence of other associated systemic diseases such as retroperitoneal fibrosis.¹¹ On

Fig. 1. Algorithm for the management of autoimmune pancreatitis.

the contrary, there appears to be no role for steroids in patients who are presented in the post-acute phase with pancreatic atrophy.¹⁵

While most AIP patients get biliary stenting during the work-up of the jaundice, there are some patients whose jaundice is relieved by steroid therapy alone without need for stenting.¹⁶ It is unclear if biliary obstruction can be treated with steroid therapy alone without need for stenting before steroids are given.¹⁶ If a biliary stent is placed on presentation of biliary strictures, stent removal is possible 2 months after starting steroids in the majority of patients.

2. Steroid regimen

The flow sheet (Fig. 1) shows treatment strategy in our institution for the treatment of AIP. Following diagnosis, induction dose of prednisolone is started. Response to steroids is assessed in terms of pre- and poststeroid symptoms, liver biochemistry, serum IgG/IgG4 levels and radiological appearances. After confirmation of clinical remission, prednisolone is gradually reduced to the maintenance dose. Maintenance therapy with low-dose steroids is used to prevent disease relapse and maintain remission. Finally, steroids are usually completely discontinued.

Till now, steroid regimen for AIP has not been standardized and there is no consensus on the dose and duration of induction steroids, tapering schedule, and optimal duration and dose of maintenance therapy. Starting dose of prednisolone for induction of remission ranges from 30 to 40 mg in most studies.¹⁷⁻²⁰ In some studies, however, starting doses were daily use of 50-60 mg of prednisolone.¹⁴ Induction doses are typically given for 1 month followed by a taper of varying duration. In the Mayo Clinic, prednisolone is used at 40 mg/day for 4 weeks and is tapered thereafter by 5 mg/week for a total of 11 weeks of therapy.¹⁷ This is relatively a short course of steroids compared to other authors. In the Mayo Clinic, maintenance therapy was restricted to those who relapsed. In Asan Medical Center, remission is achieved on a regimen of prednisolone 0.5 mg/kg per day for 1-2 months followed by a gradual taper of 5-10 mg per month to the maintenance dose of 2.5-7.5 mg/day, which was continued for an average of 6 months and then completely stopped.²⁰ In Japan, the preferred initial dose of prednisolone is 30-40 mg/day, and it is tapered by 5 mg by every 1-2 weeks.^{11,21} Patients in whom complete radiological improvement is documented stop their medication, but most patients require continued maintenance therapy with prednisolone 5 mg/day.²²

Maintenance therapy involves the use of immunosuppressive therapy to prevent disease relapse and main-

tain remission. Whether maintenance therapy should be used in all patients or restricted to those who relapse or are likely to relapse after initial steroid course remains to be established.³ The high frequency of disease relapses has led many Japanese investigators to maintain patients on low-dose daily prednisolone (2.5-10 mg) over the long-term.¹⁹ The duration of maintenance therapy has not been established. An issue requiring further investigation will be the optimal duration of maintenance, as continued corticosteroid therapy may reduce relapse but may also increase the risk of steroid-induced adverse events. Some authors have preferred to continue low-dose steroids lifelong in all AIP patients even after achievement of complete remission. On the other hand, some investigators completely discontinue maintenance steroids after a period of about 6-12 months of treatment.²¹ Another Japanese investigator suggests maintenance steroids should be given at least for three years because it is within this period recurrences mostly occur. As for doses of steroids for maintenance therapy, studies of low-dose steroids in rheumatological diseases suggest that doses less than 7.5 mg daily have fewer side effects than higher doses.²³ However, this remains controversial because mean patient age in these studies was younger than typically seen in AIP.

The choice of maintenance therapy (low-dose steroids vs. other immunomodulatory agents) on relapse has not been established.¹⁵ In the Mayo Clinic,¹⁵ instead of using long-term low-dose steroids, they have opted to use azathioprine (2 mg/kg daily) for maintenance of remission in patients with relapse after steroid withdrawal. The choice of drug for maintenance of remission needs further studies with larger numbers of patients to assess the risk/benefit ratio (preventive effect for relapse vs. side effect of medication) of each approach. According to a recent report,²⁴ a patient with AIP and IgG4-associated cholangitis refractory to steroids and 6-mercaptopurine was treated solely with rituximab. Rituximab is a chimeric monoclonal antibody directed against CD 20, a phosphoprotein expressed on the surface of B lymphocytes. The mechanism of action of rituximab is presumed to be B-cell depletion, resulting in decreased production of pathogenic autoantibodies. Rituximab may be a treatment option for patients with refractory or recurrent AIP or IgG4-associated cholangitis.²⁴

RELAPSE

The relapse after remission of AIP is not uncommon. Relapses of AIP after remission with steroids usually occur in about one third of the patients.¹⁶ Sometimes, pan-

creas can be saved and only extrapancreatic organ is involved (Fig. 2). It appears that symptoms due to biliary strictures may be the most common clinical manifestation on relapse.¹⁶ Patients experience relapse of AIP, either during maintenance steroid therapy or after a complete discontinuation of steroids.²⁵

According to our study,²⁰ during median follow-up period of 40 months, 13 of 40 patients (33%) experienced relapse of AIP. Seven of the 13 patients experienced relapse on the maintenance dosage of prednisolone (2.5-7.5 mg/day) and the remaining 6 patients experienced relapse while off steroids. On relapse, they all responded again to

high-dose prednisolone. For these patients with relapse, maintenance therapy with steroids was given with longer duration and higher dose than that of the initial maintenance therapy.

Clinical implications of AIP relapse are as follows. More than half of patients experiencing multiple relapses had pancreatic calcifications or stones.²⁶ With multiple relapses, AIP may result in irreversible damage with intense fibrosis in a similar development to that of usual chronic pancreatitis.²⁷ Although AIP patients with first relapse respond steroids again, this late stage of AIP with multiple relapses may not show steroid responsiveness. For better

Fig. 2. Serial images of a 67-year-old man with AIP. First attack: (A, B) Before steroid therapy, CT scans show diffuse pancreatic enlargement and ERCP show narrowing (arrow) of the distal common bile duct (CBD) and dilatation of the proximal CBD. (C, D) After steroid therapy, pancreatic enlargement improves with resolution of CBD dilatation. On relapse: (E) Before steroid therapy, MRCP shows multifocal strictures at the hilar and intrahepatic bile ducts without pancreatic duct involvement. (F) After steroid retreatment, multifocal biliary strictures are being resolved. AIP, autoimmune pancreatitis.

prognosis of AIP, therefore, earlier diagnosis and treatment are essential.

1. Predictors of relapse

The identification of clinical and/or genetic predictors of relapse of AIP may be crucial to the prognosis and clinical outcome of the disease. Identification of predictors of relapse may help us to determine the high risk patients who would really benefit from maintenance therapy. For patients with AIP identified as having predictors of relapse, treatment strategy may need to be adjusted by including higher dose or longer administration of maintenance steroid therapy or additional treatment with another immunosuppressive agent. Also, closer follow-up may be needed for these patients.

1) Clinical predictor

Hirano *et al.*¹³ analyzed multiple factors for unfavorable events. They were age, sex, obstructive jaundice, abdominal pain, diffuse pancreatic ductal change, serum IgG4 level and corticosteroid therapy. Serum IgG4 levels at onset showed no correlation with prognosis. Obstructive jaundice and corticosteroid treatment retained significance as independent predictive factors on multivariate analysis. They concluded that corticosteroid therapy could reduce AIP-related unfavorable events and recommended the early introduction of corticosteroid therapy especially for patients with obstructive jaundice. On the other hand, Park *et al.*²⁰ analyzed the clinical predictors of relapse of AIP. Age, sex, body weight loss, diabetes mellitus, obstructive jaundice, amylase/lipase level, initial serum IgG/IgG4 level, and existence of other organ involvement had no correlation with relapse. In one Japanese study, like our study results, no specific clinical predictors of relapse have been identified at the time of initial diagnosis.²⁶ Kubota *et al.*²⁸ compared clinicopathologic parameters in patients with or without relapse. On the univariate analysis, serum IgG level, diffuse pancreas swelling and bile duct stricture were significantly associated with relapse. On the multivariate analysis, however, only diffuse pancreatic swelling independently predicted a relapse of AIP. Ghazale *et al.*²⁹ reported that factors predicting relapse were increased IgG4 levels and the presence of proximal biliary strictures. Patients age, sex, obstructive jaundice and proportion whose serum IgG4 normalized after treatment did not differ between relapsers and nonrelapsers. Further study about clinical predictor of relapse is needed.

2) Genetic predictor

Recently, substitution of aspartic acid to nonaspartic

acid (e.g. alanine, valine, and serine) at DQ β 1 57 is reported to be a genetic predictor for relapse of AIP.²⁰ A plausible explanation regarding the pathogenetic role of substitution of aspartic acid at DQ β 1 57 on relapse of AIP is as follows. DQ β 1 residue 57 is located near one end of the peptide-binding groove of class II molecule, where it functions as a molecular gatekeeper for the peptide side chain at the peptide binding pockets termed P9. There is a positively charged arginine residue at position 76 of the DQ α -chain adjacent to P9, and if the peptide side chain carries a negative charge such as aspartic acid, strong and stable salt bridge is formed and antigen-antibody immune reaction does not occur. When DQ β 1 residue 57 is a small noncharged residue such as alanine, however, autoantigens are able to occupy P9. As such, HLA high-resolution genotyping with amino acid sequence analysis may be useful in identifying the subgroup of individuals who are at a potentially greater risk for relapse of AIP. Interestingly, pemphigus vulgaris, bullous pemphigoid and atopic dermatitis are also known to be associated with high serum IgG4 concentrations as in AIP,³⁰⁻³² substitution of amino acid at residue 57 of DQ β 1 is reported to have a critical role in the susceptibility of their diseases. Recently, Japanese group investigated the role of cytotoxic T-lymphocyte antigen 4 (CTLA4) polymorphisms in the relapse of AIP. The +49A/A and +6230A/A genotype were associated with an enhanced risk of relapse.³³ These findings strongly suggest that regulatory functions of T cells, such as CTLA4 and CD4⁺CD25⁺ regulatory cells, are involved in the development and pathophysiology of AIP.³⁴

FOLLOW-UP

To identify relapses early, periodic follow-up of patients who have initially responded to treatment is recommended. Follow-up observations should include biochemical examinations of blood findings such as IgG4, imaging findings and clinical manifestations such as jaundice and abdominal discomfort.²¹ Although singly tested serum IgG4 levels in the initial diagnosis are not likely to sufficiently informative for the prediction of relapse, changes in serum IgG4 levels during serial check-up may give clinically useful information. In our experience (unpublished data, 2008), all relapsed patients had a rise in serum IgG4 levels to above the upper limit of normal immediately prior to relapse. The follow-up protocol of the Mayo Clinic is largely based on the organ involved. In patients with biliary strictures, laboratory testing (liver enzyme, serum IgG4) is repeated every 12 weeks for the first 1-2 years. In patients without biliary diseases, they have

monitored patients for recurrent symptoms and only then do they consider imaging.¹⁵ In the study by Hirano *et al.*,¹³ imaging was performed every 6 months with laboratory testing every 3-6 months to assess for relapse. The optimal imaging modality and interval for follow-up have not been established. In one study from the United Kingdom, instead of ERCP examination, MRCP was used to demonstrate pancreatic and biliary lesions in patients without obstructive jaundice.⁶ If the diagnostic accuracy of MRCP for the follow-up of ductal changes in AIP patients is confirmed, MRCP will be a much more suitable follow-up tool than ERCP as it is noninvasive and safer than ERCP.

Recently, there have been reports in the literature of pancreatic cancer complicating AIP years after its diagnosis.³⁵⁻³⁷ It is unclear if subsequent development of pancreatic cancer represents a true complication of longstanding AIP or a chance occurrence in an elderly man who also happened to have AIP.³⁵ Long-term studies in large cohorts of AIP are needed to determine if AIP predisposes to subsequent development of pancreatic cancer because cancer typically occurs decades after onset of chronic pancreatitis.³⁵

CONCLUSIONS

Although significant advances have been made in our understanding on the diagnosis of AIP, knowledge of optimum treatment regimen and predictive factors of relapse is still a long way to go. Making a consensus on optimal treatment regimen is very important because it could in turn lead to low relapse rate. Consensus definitions for treatment outcome should be established. Further research in this field is required.

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