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Manuscript ID:

Dear Executive Managing Editor of *the World Journal of Clinical Cases*

We appreciate your kind review of our manuscript entitled "**The challenge for clinician in autoimmune pancreatitis: current perspective**" and the suggestions raised during its review. These suggestions have been addressed, and the corresponding modifications have been made to the manuscript in response to the reviewers' comments. A point-by-point response to the reviewers' comments is enclosed.

We hope that the revised manuscript is satisfactory for publication in *the World Journ al of Clinical Cases.*

Thank you very much for your time and consideration.

Sincerely,

Hyung Ku Chon, M.D., Ph.D.

Answers to specific comments

Reviewers' comments:

Reviewer 1:

1. Please address biomarkers other than IgG4 in short. This reviewer would not agree that ANA are helpful in identifying AIP in some cases (rows 206-207), as ANA is rather a non-specific marker of autoimmunity, thus considered obsolete for AIP diagnosis.

Answer: Thank you for your comments. In the Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2018, it was reported that ANA or RF may be helpful in some patients with suspected presence of AIP. The paper you recommended also states that other non-specific markers of autoimmunity, such as antinuclear antibodies and rheumatoid factors, show variable prevalence in the sera of patients with AIP. Of course, ANA or RF are not specific to AIP, but if you suspect AIP, I think it can be helpful. We will also add your recommendations to avoid misunderstandings and include up-to-date knowledge.

DIAGNOSIS 3) serology (Rows 223-233)

Autoantibodies such as antinuclear antibodies (ANA), rheumatoid factor (RF) may be positive in some cases of AIP.(35) However, despite the current research on several biomarkers (e.g. ANA, RF, lactoferrin, carboanhydrase II, plasminogen-binding protein, amylase-α2A, cationic (PRSS1) and anionic (PRSS2) trypsinogens, pancreatic secretory trypsin inhibitor (PSTI/SPINK1), and type IV collagen, etc.) for the diagnosis of AIP, their specificity and sensitivity for the diagnosis of AIP seem to be insufficient.(75) Among them, serum IgG4 level is the most important marker for establishing the diagnosis of type 1 AIP. IgG4 levels are not sufficiently correlated with the onset of complication or recurrence.(11, 76, 77)

Reviewer: 2

1. Specific Comments to Authors: Authors should include a brief paragraph/point indicating the main limitations observed in the field. Also it will be desiderable to include their expert clinical opinion. What are the advantages and novelty of their manuscript compared to those of Khandelwal A et al., 2020 (PMID: 31650376), Goyal S et al., 2021 (PMID: 34135159) or Okazaki K, et al., 2017 (PMID: 28027896).

Answer: Thank you for your advice. We are trying to improve our paper by editing a s excellent reviewers' comments. The purpose of the review article is to summarize th e contents of the AIP so far, and there is no big difference in the contents from othe r review articles, but the contents have been organized so that the clinician can acces s it easily.

Reviewer: 3

1. I suggest inclusion of the following topics to improve the quality of the manus cript: In this kind of article, it is the most important to emphasize following:

- IgG4 serum level alone lacks sensitivity and specificity but can be helpful to es tablish the diagnosis of AIP type 1, and therefore should be measured if IgG4-rel ated gastrointestinal disease is suspected (normal serum IgG4 does not exclude AI P type 1).
- IgG4 serum levels seem to have diagnostic value when the level is higher than four times the upper level of normal, which is the case in only a minority of pat ients

Answer: I appreciate your advice. The referenced paper states that when the cut-off le vel was set at 2.8 mg/ml, specificity increased to 96%, whereas sensitivity was lost, a nd the positive predictive value was less than 50%. In our manuscript, there is a cont ent that the sensitivity is high when it is increased by more than 2 times. We will a dd that what you said lacks sensitivity and specificity.

DIAGNOSIS 3) serology (Rows 219-232)

Serum IgG4 elevations greater than twice the upper limit of the standard (>280 mg/d L) are highly specific for AIP (specificity increased to 96%), but with a positive pred ictive value of less than 50%.(4, 65-69) This is due to the presence of elevated IgG4 levels in approximately 10% of patients with PDAC or other diseases (e.g. parasitic diseases, chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis, or Sjogren's syndrome).(4, 35, 65, 70-74) Autoantibodies such as antinuclear antibodie s (ANA), rheumatoid factor (RF) may be positive in some cases of AIP.(35) However, despite the current research on several biomarkers (e.g. ANA, RF, lactoferrin, carboa nhydrase II, plasminogen-binding protein, amylase-α2A, cationic (PRSS1) and anionic (PRSS2) trypsinogens, pancreatic secretory trypsin inhibitor (PSTI/SPINK1), and type I V collagen, etc.) for the diagnosis of AIP, their specificity and sensitivity for the diag nosis of AIP seem to be insufficient.(75) Among them, serum IgG4 level is the most important marker for establishing the diagnosis of type 1 AIP. IgG4 levels are not suf ficiently correlated with the onset of complication or recurrence.(11, 76, 77)

- As with its poor quality in establishing the diagnosis of IgG4-related disease ser um, IgG4 levels cannot contribute to accurately monitoring disease course, nor do es it sufficiently correlate with the development of complications or even with rel apse

Answer: I appreciate your advice. We have added the following sentences to the man uscript.

DIAGNOSIS 3) serology (Rows 230-232)

IgG4 levels are not sufficiently correlated with the onset of complication or recurrenc e.(11, 76, 77)

- Although an increased IgG4 plasma cell count is an important finding, it is not diagnostic of AIP type 1 if found in isolation
- A biopsy showing little, or no evidence of AIP cannot be used in isolation to ex clude this diagnosis, unless a positive alternative diagnosis can be made
- For the diagnosis of AIP, the number of IgG4+ plasma cells should exceed 50 c ells/high-power field (HPF) in surgical specimens and 10 cells/HPF in biopsy sam ples (average of counts in three hot spots. In addition, the IgG4/IgG ratio should be more than 40%.

Answer: I appreciate your advice. We have added the following sentences to the man uscript.

CLASSIFICATION AND HISTOPATHOLOGICAL FEATURES (Rows 92-96)
The European guidelines recommend that the number of IgG4 positive plasma cells sh ould exceed 50 cells/HPF in surgical specimens and 10 cells/HPF in biopsy specimens (average of 3 hotspots [400x]) for the diagnosis of type I AIP, and the IgG4/IgG rat io should be at least 40%.(11) However, an increased number of IgG4 plasma cells al one are limiting the diagnosis of AIP type 1.(12, 13)

2. Other comments:
- Pancreatic exocrine insufficiency and diabetes mellitus occur commonly in AIP.
Answer: I appreciate your advice. We have added the following sentences to the man uscript.

CLINICAL MANIFESTATIONS (Row 125-130)
According to a systematic review, the pooled estimate for the prevalence of diabetes at the time of diagnosis of type 1 AIP was 44%, which was 11% higher than that of type 2 AIP.(21) In addition, the pooled estimated prevalence of exocrine insufficiency at the time of diagnosis of AIP was 45%, which means that more than one-third of

patients with AIP have significant impairment of their pancreatic function.

-AIP type 2 is just barely mentioned. AIP NOS is not mentioned – it is a part o f ICDC classification 1-2 in the sub-title

Answer: I appreciate your advice. NOS has a very small number of patients, shares s imilar clinical features with AIP type 2, and is sometimes classified as AIP type 2 du ring follow-up, so it has not been dealt with clinically. We have added the following sentences to the manuscript.

CLASSIFICATION AND HISTOPATHOLOGICAL FEATURES (Rows 104-107)
According to the ICDC, AIP type not otherwise specified (NOS) is defined as the abs ence of histological criteria and inflammatory bowel disease. AIP type NOS is rarely diagnosed, and some studies have reported that AIP NOS has clinically similar charact eristics to type 2 AIP and can be converted to type 2 AIP.(16, 17)

- **you use abbreviation ERCP and in the text ERP**

Answer: Thank you for your attentive observation. The manuscript was integrated into ERCP and corrected. (Row 164, 165)

- **What is the role of surgery in AIP?**

Answer: I appreciate your advice. We have added the following sentences to the man uscript.

***2) Endoscopic ultrasound-guided fine needle aspiration (FNA) and fine needle biops y (FNB)* (Rows 210-212)**

Surgery may be considered for patients whose suspicion of malignant/premalignant lesi ons cannot be excluded even after detailed diagnostic workup such as biopsy through EUS or ERCP.(62)

Reviewer: 4
1. Recently, cases of pancreatic cancer or cholangiocarcinoma complicating autoim mune pancreatitis have been reported. We recommend additional references and discussion of the association with these malignancies.

Answer: I appreciate your advice. We have added the following sentences to the man uscript.

PROGNOSIS (Row 328-333)
Chronic pancreatitis was progressed 22% of the patients with AIP and approximately

40% of the patients developed pancreatic stones..(125, 126) Chronic pancreatitis is a r isk factor for PDAC, but studies on the incidence of PDAC in AIP patients have rep orted conflicting results.(124, 127, 128) Additional research is required since a case re port indicates that PDAC and cholangiocarcinoma developed during follow-up after aut oimmune pancreatitis treatment.(129, 130)

2. The most important question for the patient is whether AIP is a life-threatenin g disease. More discussion of life prognosis is needed.

Answer: I appreciate your advice. We have added a PROGNOSIS chapter on prognosi s to our manuscript.

Row 317-333
PROGNOSIS

There may be an increased risk of endocrine and exocrine insufficiency in AIP patient s. The pooled estimated prevalence of diabetes at the time of diagnosis of AIP patient s was 37% and the pooled estimated prevalence of diabetes at follow-up in AIP patie nts with or without steroid treatment was 42% and 44%, respectively..(21) An increas ed prevalence of diabetes is also reported in patients receiving long-term steroid thera py..(123) The pooled prevalence of exocrine pancreatic insufficiency in AIP patients tr eated with steroids was 36%, which was improved from the time of diagnosis (45%). However, verification is warranted as other studies report an additional risk of exocri ne pancreatic insufficiency during follow-up in patients with AIP.(123) About 14% to 26% of the patients with AIP developed malignancy. Most were detected within 1 yea r or at the time of the diagnosis and occurred more in other organs such as the stom ach, lung and prostate than the pancreas.(124) Chronic pancreatitis was progressed 2 2% of the patients with AIP and approximately 40% of the patients developed pancre atic stones..(125, 126) Chronic pancreatitis is a risk factor for PDAC, but studies on t he incidence of PDAC in AIP patients have reported conflicting results.(124, 127, 128) Additional research is required since a case report indicates that PDAC and cholangi ocarcinoma developed during follow-up after autoimmune pancreatitis treatment.(129, 1 30)

3. It is well known that in AIP, steroid treatment improves pancreatic swelling a nd decreases serum IgG4 levels. So, does it also improve the exocrine and endocr ine functions of the pancreas?

Answer: I appreciate your advice. We have added the following sentences to the man uscript.

PROGNOSIS (Row 318-326)

There may be an increased risk of endocrine and exocrine insufficiency in AIP patient s. The pooled estimated prevalence of diabetes at the time of diagnosis of AIP patient s was 37% and the pooled estimated prevalence of diabetes at follow-up in AIP patie nts with or without steroid treatment was 42% and 44%, respectively..(21) An increas ed prevalence of diabetes is also reported in patients receiving long-term steroid thera py..(123) The pooled prevalence of exocrine pancreatic insufficiency in AIP patients tr eated with steroids was 36%, which was improved from the time of diagnosis (45%). However, verification is warranted as other studies report an additional risk of exocri ne pancreatic insufficiency during follow-up in patients with AIP.(123)

4. In AIP with biliary obstruction, bile duct stenting via ERCP is performed. Ho wever, is stenting necessary in all obstruction cases? Is it acceptable to start ster oid therapy first? Please indicate the treatment strategy for AIP complicated with obstructive jaundice.

Answer: I appreciate your advice. We have added the following sentences to the man uscript.

TREATMENT (Row 296-304)

In patients with AIP with obstructive jaundice, a biliary stenting was usually performe d along with biopsy through ERCP.(77, 115) Some studies have reported that obstructi ve jaundice was treated with steroid treatment without biliary stents because AIP resp onds rapidly to steroid treatment.(116, 117) However, since AIP is sometimes difficult to differentiate from pancreatic cancer or concomitant cholangiocarcinoma, empirical s teroid treatment can be challenge without insertion of a biliary stent and biopsy. In c ase of a biliary stent insertion, early biliary stent removal after diagnosis of AIP acco rding to the guideline should be considered due to stent related complications such as migration or stent dysfunction.

October 31, 2022

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Answers to specific comments

Reviewers' comments:

Reviewer 1:

1. Please address biomarkers other than IgG4 in short. This reviewer would not agree that ANA are helpful in identifying AIP in some cases (rows 206-207), as ANA is rather a non-specific marker of autoimmunity, thus considered obsolete for AIP diagnosis.

Answer: Thank you for your comments. We have included up-to-date knowledge.

DIAGNOSIS 3) serology (Rows 236-251)

- *The c-ANCA tends to be increased in some patients with type 2 AIP, which may help distinguish type 1 from type 2. However, despite the current research on various biomarkers (e.g. antibody against carboanhydrase II, antibody against plasminogen-binding protein, antibody against lactoferrin, antibody against Alpha 2A amylase, antibodies against cationic (PRSS1) and anionic (PRSS2) trypsinogens, and pancreatic secretory trypsin inhibitor (PSTI/SPINK1) antibodies, etc.) for the diagnosis of AIP and differentiation from PDAC, verification of specificity and sensitivity for commercialization is still insufficient.*
- *Elevation of carbohydrate antigen (CA) 19-9 levels are commonly observed in pancreatic cancer (sensitivity of 79-95%, specificity of 82-91%), but up to 38% of patients with AIP have values > 100 U/mL. Therefore, the measurement of CA 19-9 or IgG4 alone is not sufficient to differentiate between AIP and PDAC, but one study reported that the combination of IgG4 of > 100 mg/dL and CA19-9 of < 74 U/mL was more likely to be AIP than PDAC (sensitivity of 94%, specificity of 100%). In addition, serum eosinophilia, raised total serum IgE levels, and serum micro RNAs can be used to differentiate between AIP and PDAC.*

Reviewer: 2

1. Specific Comments to Authors: Authors should include a brief paragraph/point indicating the main limitations observed in the field. Also it will be desiderable to include their expert clinical opinion. What are the advantages and novelty of t heir manuscript compared to those of Khandelwal A et al., 2020 (PMID: 3165037 6), Goyal S et al., 2021 (PMID: 34135159) or Okazaki K, et al., 2017 (PMID: 28 027896).

Answer: Thank you for your advice. We tried to improve it by editing the thesis. Thr ough various suggestions, methods to solve the difficulties of diagnosis or the necessit y of long-term follow-up were additionally explained.

- *Diagnosis of AIP is still challenging even with imaging, histological, and serolo gical tests. Therefore, follow-up with a thorough clinical history and physical ex amination is required. In the case of type 1 AIP, additional imaging tests can b e considered to determine whether other organs involvement, and in the case of type 2 AIP, the presence or absence of IBD can be confirmed through colonos copy. If AIP is suspected, but a definitive diagnosis is not possible despite sever al tests, and no malignancy is found in histopathological examination, the impro vement of the lesion can be confirmed after an empirical short-term (2 weeks) s teroid treatment.[86] If the lesion worsens on follow-up imaging after 2 weeks, a biopsy can be performed again and surgical treatment can be considered if n ecessary. However, applying a steroid trial to patients in whom differentiation fr om malignancy is an issue could result in delayed pancreatic cancer surgery an d subsequent cancer progression, so sufficient information should be provided to the patient. In addition, novel biomarkers that have recently attracted attention may help distinguish PDAC from AIP.*

Reviewer: 3

1. I suggest inclusion of the following topics to improve the quality of the manus cript: In this kind of article, it is the most important to emphasize following:

- IgG4 serum level alone lacks sensitivity and specificity but can be helpful to es tablish the diagnosis of AIP type 1, and therefore should be measured if IgG4-rel ated gastrointestinal disease is suspected (normal serum IgG4 does not exclude AI P type 1).
- IgG4 serum levels seem to have diagnostic value when the level is higher than four times the upper level of normal, which is the case in only a minority of pat ients

Answer: I appreciate your advice. We have edited the manuscript to the following sen tence.

DIAGNOSIS 3) serology (Rows 222-230)

- Serum IgG4 elevations greater than twice the upper limit of the standard (>280 mg/dL) are highly specific for AIP (specificity increased to 96%), but with a pos itive predictive value of less than 50%. This is due to the presence of elevated Ig G4 levels in approximately 10% of patients with PDAC or other diseases (e.g. pa rasitic diseases, chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis, or Sjogren's syndrome). In addition, although LPSP with typical IgG4 + plasma cell abundance, a histological finding of type 1 AIP, was observed, the level of IgG4 in serum was sometimes lower than the cutoff value, so the level of IgG4 did not rise in all type 1 AIP patients.

- As with its poor quality in establishing the diagnosis of IgG4-related disease ser um, IgG4 levels cannot contribute to accurately monitoring disease course, nor do es it sufficiently correlate with the development of complications or even with rel apse

Answer: I appreciate your advice. We have added the following sentences to the man uscript.

DIAGNOSIS 3) serology (Rows 231-235)

- The patients with increased IgG4 concentrations have high disease activity, a hi gh incidence of jaundice at onset, and a number of extrapancreatic manifestations.

[74, 75] However, IgG4 levels are not sufficiently correlated with the onset of complication or recurrence.[11, 74, 76, 77] Therefore, serological markers such as autotaxin are being studied for their relevance to relapse.[78]

- Although an increased IgG4 plasma cell count is an important finding, it is not diagnostic of AIP type 1 if found in isolation
- A biopsy showing little, or no evidence of AIP cannot be used in isolation to exclude this diagnosis, unless a positive alternative diagnosis can be made
- For the diagnosis of AIP, the number of IgG4+ plasma cells should exceed 50 cells/high-power field (HPF) in surgical specimens and 10 cells/HPF in biopsy samples (average of counts in three hot spots. In addition, the IgG4/IgG ratio should be more than 40%.

Answer: I appreciate your advice. We have added the following sentences to the manuscript.

CLASSIFICATION AND HISTOPATHOLOGICAL FEATURES (Rows 92-96)

- *The European guidelines recommend that for the diagnosis of type 1 AIP, the number of IgG4+ plasma cells should exceed 50 cells/HPF in surgical specimens and 10 cells/HPF in biopsy specimens (average of 3 hotspots [400x]), and also, the IgG4/IgG ratio should be at least 40%.(11) However, an increased number of IgG4 plasma cells alone are limiting the diagnosis of AIP type 1.(12, 13)*

- Authors did not mention risk of pancreatic cancer in AIP and in IgG4 in general. How these patients (AIP) are followed?

Answer: I appreciate your advice. We have added the following sentences to the manuscript.

PROGNOSIS (Row 373-388)

- *Patients with AIP may be associated with an increased risk of developing malignant disease compared to the general population. A significant number of AIP patients were diagnosed with cancer at the time of AIP diagnosis or within 1 year, and occurred more in other organs such as the stomach, lung and prostate than the pancreas. These results suggest that AIP may be related to cancer in other organs than the pancreas itself. Based on this phenomenon, some studies have argued that because cancer and AIP occur simultaneously, AIP can sometimes occur in coexisting cancer as paraneoplastic syndrome. Studies on the incidence of PDAC in AIP patients have reported conflicting results. Additional researc*

h is required since a case report indicates that PDAC and cholangiocarcinoma developed during follow-up after autoimmune pancreatitis treatment. Studies on p atients with IgG4-related diseases have also shown that various malignant disea ses (lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, lymphoma, leukemia, etc.) occur, which suggests that IgG4-related diseases are associated with an increased risk of malignant disease. Although it is still controversial wh ether AIP is a risk factor for malignancy, it should not be overlooked that care ful attention to the occurrence of malignancy is required at the time of AIP dia gnosis and during follow-up.

2. Other comments:
- Pancreatic exocrine insufficiency and diabetes mellitus occur commonly in AIP.

Answer: I appreciate your advice. We have added the following sentences to the man uscript.

CLINICAL MANIFESTATIONS (Row 125-130)

- *According to a systematic review, the pooled estimate for the prevalence of DM at the time of diagnosis of type 1 AIP was 44%, which was 11% higher than that of type 2 AIP. In addition, the pooled estimated prevalence of exocrine insu fficiency at the time of diagnosis of AIP was 45%. Thus, DM and pancreatic ex ocrine insufficiency that occurs in AIP means that more than one-third of patien ts with AIP have significant impairment of their pancreatic function.*

-AIP type 2 is just barely mentioned. AIP NOS is not mentioned – it is a part o f ICDC classification 1-2 in the sub-title

Answer: I appreciate your advice. NOS has a very small number of patients, shares s imilar clinical features with AIP type 2, and is sometimes classified as AIP type 2 du ring follow-up, so it has not been dealt with clinically. We have added the following sentences to the manuscript.

CLASSIFICATION AND HISTOPATHOLOGICAL FEATURES (Rows 104-107)

- *According to the ICDC, AIP type not otherwise specified (NOS) is defined as th e absence of histological criteria and inflammatory bowel disease. Type NOS AI P is rarely diagnosed, and some studies have reported that type NOS AIP has clinically similar characteristics to type 2 AIP and can be converted to type 2 AIP.*

- **you use abbreviation ERCP and in the text ERP**

Answer: Thank you for your attentive observation. The manuscript was integrated into ERCP and corrected.

- **What is the role of surgery in AIP?**

Answer: I appreciate your advice. We have added the following sentences to the man uscript.

2) Endoscopic ultrasound-guided fine needle aspiration (FNA) and fine needle b iopsy (FNB) **(Rows 210-215)**

- *Diagnosis of AIP is not always simple and in some cases it is not easy to disti nguish it from pancreatic cancer, and the prevalence of concomitant pancreatic t umors (benign and malignant) in AIP patients has been documented in up to 7% of cases. Therefore, Surgery may be considered for patients whose suspicion of malignant/premalignant lesions cannot be excluded even after detailed diagn ostic workup such as biopsy through EUS or ERCP.*

Reviewer: 4

1. Recently, cases of pancreatic cancer or cholangiocarcinoma complicating autoimmune pancreatitis have been reported. We recommend additional references and discussion of the association with these malignancies.

Answer: I appreciate your advice. We have added the following sentences to the manuscript.

PROGNOSIS (Row 373-388)

- *Patients with AIP may be associated with an increased risk of developing malignant disease compared to the general population. A significant number of AIP patients were diagnosed with cancer at the time of AIP diagnosis or within 1 year, and occurred more in other organs such as the stomach, lung and prostate than the pancreas. These results suggest that AIP may be related to cancer in other organs than the pancreas itself. Based on this phenomenon, some studies have argued that because cancer and AIP occur simultaneously, AIP can sometimes occur in coexisting cancer as paraneoplastic syndrome. Studies on the incidence of PDAC in AIP patients have reported conflicting results. Additional research is required since a case report indicates that PDAC and cholangiocarcinoma developed during follow-up after autoimmune pancreatitis treatment. Studies on patients with IgG4-related diseases have also shown that various malignant diseases (lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, lymphoma, leukemia, etc.) occur, which suggests that IgG4-related diseases are associated with an increased risk of malignant disease. Although it is still controversial whether AIP is a risk factor for malignancy, it should not be overlooked that careful attention to the occurrence of malignancy is required at the time of AIP diagnosis and during follow-up.*
-

2. The most important question for the patient is whether AIP is a life-threatening disease. More discussion of life prognosis is needed.

Answer: I appreciate your advice. We have added a PROGNOSIS chapter on prognosis to our manuscript.

3. It is well known that in AIP, steroid treatment improves pancreatic swelling and decreases serum IgG4 levels. So, does it also improve the exocrine and endocrine functions of the pancreas?

Answer: I appreciate your advice. We have added the following sentences to the manuscript.

PROGNOSIS (Row 350-372)

- *In patients with AIP, the prevalence of endocrine and exocrine insufficiency at the time of AIP diagnosis is high. In a recent meta-analysis, the pooled estimate rate for the overall prevalence of DM in patients at the time of AIP (combined type 1 and type 2 AIP) diagnosis was 37%.[21] At the time of AIP diagnosis, the prevalence of DM was higher in Asian countries than in Western countries, and the pooled estimate of prevalence of DM was 44% in type 1 AIP and 11% in type 2 AIP. The pooled estimated prevalence of diabetes at follow-up in AIP patients with or without steroid treatment was 42% and 44%, respectively.[21] In studies conducted in Asian and Western countries, respectively, the pooled estimate rate of DM at follow-up was 49% and 34%. In some studies, glycemic control was improved by steroid treatment when AIP was accompanied by DM[116-118], but in a meta-analysis, the prevalence of DM increased during long-term follow-up.[21, 131] The pooled prevalence of exocrine pancreatic insufficiency in AIP patients treated with steroids was 36%, which was improved from the time of diagnosis (45%). However, verification is warranted as other studies report an additional risk of exocrine pancreatic insufficiency during follow-up in patients with AIP.[131] Histological analysis, as well as changes in pancreatic volume, structure or obstruction of the main pancreatic duct, and decreased stimulation of the exocrine, suggest that islet cells in AIP patients are fibrosis and lymphoplasmatic cell infiltration is associated with endocrine and exocrine insufficiency of the pancreas.[132-134] Improvements in histological findings in patients with AIP after steroid treatment can sometimes lead to betterments in endocrine and exocrine function, but further studies and long-term follow-up are still required. Also, chronic pancreatitis was progressed 22% of the patients with AIP and approximately 40% of the patients developed pancreatic stones,[135, 136] the occurrence of chronic pancreatitis-related complications is also expected to inc*

rease.

4. In AIP with biliary obstruction, bile duct stenting via ERCP is performed. However, is stenting necessary in all obstruction cases? Is it acceptable to start steroid therapy first? Please indicate the treatment strategy for AIP complicated with obstructive jaundice.

Answer: I appreciate your advice. We have added the following sentences to the manuscript.

TREATMENT (Row 328-336)

- *In patients with AIP with obstructive jaundice, a biliary stenting was usually performed along with biopsy through ERCP.[77, 123] Some studies have reported that obstructive jaundice was treated with steroid treatment without biliary stents because AIP responds rapidly to steroid treatment.[124, 125] However, since AIP is sometimes difficult to differentiate from pancreatic cancer or concomitant cholangiocarcinoma, empirical steroid treatment can be challenge without insertion of a biliary stent and biopsy. In case of a biliary stent insertion, early biliary stent removal after diagnosis of AIP according to the guideline should be considered due to stent related complications such as migration or stent dysfunction.*