Dear editors,

thank you again for evaluating our manuscript.

We addressed all the points from the reviewers, the updated paragraphs in the manuscript are marked with red.

Unfortunately we miscalculated the time stamps of follow-up, so we corrected the intervals in table 1. Also, we now mentioned that the second to last ultrasonographic evaluation was done with a different device, so the discrepancy may be better understandable. Also this point is now mentioned in the text. All other measurements were done with the same device by the same examiner.

We would be glad if you feel our remarks and changes are sufficient and the manuscript may be worth to be published in the World Journal of Gastroenterology.

2 Peer-review report

Reviewer #1: This case report is an appreciable attempt of exploring new potential approaches to portal hypertension-related bleeding prophylaxis in cirrhotic patients, especially considering the increasing amount of paper highlighting potential pitfalls of chronic beta-blockers administration in advanced cirrhosis. In the described case, clinical and endoscopic goals of the treatment with PDE-5-inhibitors were reached, and the Authors were even able to show a clear decrease in HVPG during follow-up (although the standard decrease of > 20% was not reached). Despite this, after carefully reading the paper, I think that there are some major issue that need to be examined before any conclusion about the potential use of these drugs in this setting.

1) Which was the systemic haemodynamic effects of these drugs? Patient with cirrhotic portal hypertension usually present alteration in systemic haemodynamic (low SVR, high CO and CI…) and using a vasoactive drug (such as PDE-5-inhibitors, beta-blockers…) could lead to a haemodynamic derangement. Therefore, monitoring of systemic haemodynamics should be done while testing drugs with such vasoactive effects in this setting. If performed, data about right heart catheterization at baseline and during follow-up are very valuable. If not, data about heart rate, blood pressure and echocardiographic findings could be an acceptable surrogate

We thank Reviewer 1 for these important remarks. Indeed, PDE-5-inhibitors may influence the haemodynamics of patients, especially with liver cirrhosis. However, in several studies it has been shown that the lowering effect on systemic blood pressure is minor with regard to the induced changes in pulmonary or portal circulation. This has been shown in our previous studies with Udenafil (Dig Liver Dis. 2015 Feb;47(2):144-50.) and Vardenafil (Aliment Pharmacol Ther. 2006 Jan 1;23(1):121-8.), as in a case with portopulmonary hypertension (J Med Case Rep. 2007 Jul 10;1:46.). In this revised manuscript we emphasized these findings and added echocardiographic findings as well as heart rates and blood pressure in Table 1. These completition emphasizes the minor changes in systemic circulation in contrast to changes in portal blood flow.

2) Related to point 1, cirrhotic patients with portal hypertension with worsening of systemic haemodynamic alterations usually present an increase or a de novo appearance of ascites, not even

predictable using only HVPG value: data about clinical and echocardiographic findings are therefore crucial

To give more information regarding this point, blood pressure and heart rates are amended in Table 1. Constant echocardiographic measurements in year 2009, 2013 and 2017 are mentioned in the text. We completely agree with reviewer #1 that these are important findings that have to be emphasized.

3) The patient described presented (despite a long history of bleedings) with a quite-compensated cirrhosis, as evidenced by Child-Pugh score A. For reason mainly related to Point 2, I'm not sure that patients at a more decompensated stage of cirrhosis could tolerate these drugs as well. I think that this should be underlined in the text and lead to more cautious and single patients-oriented conclusions

This assessment is very helpful. We added these restrictions in the discussion: "*However, the potential for a beneficial or detrimental effect of PDE-5 inhibitors may depend on the stage of liver disease and the extension of portal collaterals as it has been postulated for nitrates*"

Reviewer #2: Dear Editor, In the manuscript authors shed light in the complex pathophysiological substrate of portal hypertension adding data on therapeutic approach. Therefore, I think that Manuscript can be accepted, with the following concerns.

1) If patient was diagnosed with overlap syndrome, why UDCA was not administered? Explain better.

Thank you for emphasizing this point. The patient presented clinically as autoimmune hepatitis. The laboratory results as well as the histologic findings suggested the diagnosis of AIH, there were no findings of cholestasis. However, because of the positive AMA antibody, the diagnosis was changed to overlap syndrome. As no cholestasis was apparent, no UDCA was administered, according to the actual guidelines. The lack of cholestasis is now mentioned in the manuscript (section presenting the case report).

2) No relevant effect was observed on systemic blood pressure with use of the drug. This in an important item: results should be report in text (not only " no relevant effect").

Please refer to Answer to Reviewer 1: more details are now given in the text and Table 1.

3) Case report describes a patient with a cirrhosis in Child A class. In discussion, literature debating the role of NO inhibition in different stage of liver disease should be report (cfr. angelico et al, Long-acting nitrates in portal hypertension: to be or not to be? Dig Liver Dis. 2001). Finally, I suggest authors to remark this concept also in the last sentence of abstract.

Thank you for this supplement. The concept is now mentioned in the abstract. Also see answer to Reviewer#1 Point 3.

Reviewer #3: It is an interesting case report about the role of PDE 5 inhibitors on the reduction of portal pressure in a patient with liver cirrhosis. I have only one comment to make. There is no doubt about the effect of the drug on the acute setting, as the authors showed direct reduction of HVPG after the administration of the drug. However, I have some concerns about the role of the drug on the long term. We do not have any information about liver histology. We do not know if autoimmune hepatitis was under control at the beginning or if this happened later, during the follow up. Thus, we can't be sure if the portal pressure became stable during the long term because of the drug, or because of the regression of liver damage. So it would be very important to give us some information about liver histology, or liver stiffness at the beginning of the study and during the follow up.

Histologic findings proved the diagnosis of cirrhosis. ALT and AST were mostly normal, sometimes slightly elevated during the follow-up despite the immunosuppressive therapy. We believe it is relatively improbable that cirrhosis at this stage, with an inflammatory component, would resolve or improve significantly. After cirrhosis was diagnosed in 1989 it had been stable for more than 20 years when our therapy with PDE-5-inhibitors was started. This is now mentioned in the section "Discussion": *In the presented case the diagnosis of cirrhosis had been done in 1989. The course of disease was relatively stable under immunosuppressive therapy for 20 years. However, episodes of upper gastrointestinal bleeding occurred. It is unlikely that after such a time period a spontaneous improvement in portal hypertension would occur. Echocardiographic examinations in the year 2009, 2013 and 2017 revealed constant findings. Taken together with stable values of blood pressure and heart rate no significant changes in systemic circulation were detected during the years of follow-up. Therefore, the improvement in portal hemodynamics could be attributed to the application of the PDE-5-inhibitors.*

Fibroscan was not performed.

Reviewer #4: The authors presented a case with portal hypertension due to AIH/PBC overlap syndrome, who had recurrently bled from esophageal varices and had been successfully treated by a PDE-5-inhibitor. HVPG decreased by 14% at the initial hemodynamic test and by 15% a few months later. Portal venous flow increased by 28% as measured by Doppler ultrasound and by 16% as measured by four-dimensional flow MRI. They showed that these measurements persisted for more than eight years and were accompanied by a beneficial clinical effect without any adverse effects. This manuscript appears nearly acceptable for publication, but several revisions would be considered as follows. In this paper, the authors have not taken up the ethical point of view, including informed consent. There were a few descriptions of the mechanism of a PDE-5-inhibitor how lower portal hypertension in patients with liver cirrhosis. Furthermore, they should mention the limitation of this technique.

Thank you for mentioning this point. Of course we discussed the „off-label use" with the patient and obtained a written informed consent. Since this is the first documented case of a long-term treatment of PDE-5 inhibitor in a patient with cirrhosis the experimental nature of this approach was sufficiently discussed. This is now pointed out in the manuscript: "*We discussed an experimental*

therapeutic approach of the application of a PDE-5-inhibitor with the patient. The patient was informed that this was an off-label use and gave written informed consent."