

Dear. Editor and reviewers

Journal of World Gastroenterology

We thank the reviewers for their valuable advice, and are grateful to you for all the favor you have done us.

We have responded to all the questions by the reviewers with answers or explanations, and have revised our paper accordingly. We hope they will be satisfied. But we are willing to provide further information if they think it necessary. The answer attached on the end this letter.

According to your requirements, the revision has been editing again by SinoScript, LLC, Date: 2022.08.31.

In here, we are submitting the revised manuscript '**Heterogeneity of immune control in chronic HBV infection: Clinical implications on immunity with interferon- $\alpha$  treatment and retreatment**' to you. Manuscript NO: 77634, Minireviews.

In the F6Publishing system and ORC ID, Guoqing Yin's name is spelled Guo-Qing Yin. In order to be consistent with the spelling of the other two authors, Guoqing Yin is spelled in the manuscript. However, the other two authors, Keping Chen and Xiaochun Gu, have the same spelling of their names in the F6Publishing system and ORC ID. Therefore, in the finally accepted manuscript, both spellings: Guoqing Yin or Guo-Qing Yin are optional, pending your decision.

We wish our paper be accepted and published in your journal as soon as possible.

Yours respectfully;

Authors: Guoqing Yin, Keping Chen, Xiaochun Gu

Below, we respond to peer reviewers' comments in a peer-to-peer manner.

**Reviewer's Comment:**

The overall scientific information of the manuscript is good. There are some points to be added to make the article more valuable to the readers, such as the summarized table for the outcome of INF-a treatment in CHB and also including the re-treatment strategy. Table 2 is too complex to understand and does not assist the reader in understanding the clinical implications of interferon treatment and retreatment. 3, host genetic variants associated with IFN-a therapy, which ways of the association for INF-a treatment? For table 3, the description of the abbreviation could not be understood. For table, it should be "table," not "table." It should be IFN-a retreatment for FN-a retreatment. The citation for table 3 in the text is [43,44,74-78] but in the table itself it is [43, 74, 87]. Why the difference? I recommend that the authors include the IFN-a retreatment in

"IMPROVEMENT OF HBV-SPECIFIC IMMUNE CONTROL BY IFN- RETREATMENT" and revise this section for completeness. The English grammar needed to be polished. The reference format was not precise as a whole, such as "1. Revill PA, Chisari FV, Block JM, Dandri M, Adam J Gehring , Guo H, et al. A global scientific strategy to cure hepatitis B. *Lancet Gastroenterol Hepatol* 2019; 4: 545-558. [PMCID: PMC6732795 DOI: 10.1016/S2468-1253(19)30119-0], 2 Rehmann B, Thimme R. Insights From Antiviral Therapy into Immune Responses to Hepatitis B and C Virus Infection. *Gastroenterology*. 2019; 156: 369-383. [PMID: 30267712 DOI: 10.1053/j.gastro.2018.08.061]", please recheck again.

**Comment:**

The overall scientific information of the manuscript is good. There are some points to be added to make the article more valuable to the readers, such as the summarized table for the outcome of INF-a treatment in CHB and also including the re-treatment strategy.

*Answer:*

Ok, thank reviewer's comment. The authors have added Table 4, in which 10 papers related to IFN-a retreatment are presented, including 6 clinical studies, 3 Asian-Pacific clinical practice guidelines (2008, 2012, 2016) and 1 review.

**Comment:**

Table 2 is too complex to understand and does not assist the reader in understanding the clinical implications of interferon treatment and retreatment.

*Answer:*

In chapter 2 of this manuscript, 'HETEROGENEOUS IMMUNITIES DURING HBV INFECTION', we review the mechanisms of immune response to HBV infection and present the genes associated with immunology responses. In addition, we explore the heterogeneity of HBV-specific immune control in this chapter.

In the second chapter, Section VI, 'Host genetic variations associated with HBV infection', introduces the immunological host genetic variants associated with HBV infection. Table 2 show the genes that has been conformed to impact the outcomes of HBV infection. In addition, the host genes associated with IFN-a treatment are listed in Table 3.

**Comment:**

3, host genetic variants associated with IFN-a therapy, which ways of the association for INF-a treatment?

*Answer:*

In the section, ***Host genetic variations associated with HBV infection***, we briefly describe the role of host genes in the immune response to HBV infection. In Table 2, authors show immune-related cytokines, epitopes and receptors of immune cells, inflammatory cytokines, inhibitory cytokines, HLA-associated host gene variants, et al. These host genes directly affect protein conformation, and alter the pattern and efficiency of the immune response. In addition, Table 3 presents the host genes associated with IFN- $\alpha$  efficacy.

Tables 2 and 3 show descriptive data that are not familiar to clinicians and general immunologists. After the first peer review, we attempted to delete Tables 2 and 3. However, after deletion, there is no proof that host genetics alter HBV-specific immune control or that host genes influence the efficacy of interferon. Furthermore, immunogeneticists at our university strongly opposed the deletion of Tables 2 and 3. Therefore, Tables 2 and 3 are retained.

**Comment:**

For table 3, the description of the abbreviation could not be understood. For table, it should be "table," not "table."

*Answer:*

Ok, thank you. The abbreviation, SNPs/Hap/CNVs: Single nucleotide polymorphisms/Haplotype/Copy number variations, was added to the end of Tables 2 and 3.

Table 3 is changed to

**Table 3** Host genetic variants associated with IFN- $\alpha$  therapy [43,44,74,87]

Gene ontology	Gene	Genetic determinants (SNP/Hap/CNVs)
HLA	HLA-DP	rs3077, rs9277535
	HLA-DQA1-DQB1-DRB1	*0302-*0303-*09
	HLA-DQB1	*0303
	HLA-DRB1	*08
	HLA-A, B, C	*1101-*4601-*0102
Cytokines	IL-28B	A-C <sup>1</sup> , rs8099917, rs12979860, rs12980275
Others	CYP24A1	rs2248359
	CYP27B1	rs10877012, rs4646536
	G3BP2	rs3821977
	OAS	G-T-G-A <sup>2</sup> , C-C-T-A <sup>3</sup> , C-C-C-A <sup>4</sup> , A-C-T-A <sup>5</sup>
	OAS3	rs2072136
	PRELID2	rs371991
	STAT4	rs7574865
	TRAPPC9	rs78900671
	VDBP	rs7041
	VDR	rs1544410, rs731236, rs11568820, rs10735810

*Haplotypes*

<sup>1</sup>A-C, rs12980275-rs12979860; <sup>2</sup>G-T-G-A, rs3177979-rs1293747-rs4767043-rs10849829; <sup>3</sup>C-C-T-A, rs2285934-rs2072138-rs2072136-rs10849829; <sup>4</sup>C-C-C-A, rs2285934-rs2072138-rs2072136-rs10849829; <sup>5</sup>A-C-T-A, rs2285934-rs2072138-rs2072136-rs10849829.

SNPs/Hap/CNVs: Single nucleotide polymorphisms/Haplotype/Copy number variations

#### Comment

It should be IFN- $\alpha$  retreatment for FN- $\alpha$  retreatment.

Answer:

It's a spelling error, thanks you for your correction!

#### Comment

The citation for table 3 in the text is [43,44,74-78] but in the table itself it is [43, 74, 87]. Why the difference?

Answer:

Sorry for my oversight!

The correct expression should be [43,44,74,87] in the text and the table 3.

#### Comment:

I recommend that the authors include the IFN- $\alpha$  retreatment in "IMPROVEMENT OF HBV-SPECIFIC IMMUNE CONTROL BY IFN- RETREATMENT" and revise this section for completeness.

Answer

Ok, thank you for your recommendation!

The section, *IFN- $\alpha$  retreatment*, was moved to Chapter IV, **IMPROVEMENT OF HBV-SPECIFIC IMMUNE CONTROL BY IFN- $\alpha$  RETREATMENT**, as the first section. The second section is titled: *Interplay between IFN- $\alpha$  retreatment and the HBV-specific immune control*.

#### Comment

The English grammar needed to be polished.

Answer:

Ok, the second English Editing has been completed, see Second English Editing Certificate.

#### Comment:

The reference format was not precise as a whole, such as "1. Revill PA, Chisari FV, Block JM, Dandri M, Adam J Gehring, Guo H, et al. A global scientific strategy to cure hepatitis B. Lancet Gastroenterol Hepatol 2019; 4: 545-558. [ PMID: PMC6732795 DOI: 10.1016/S2468-1253(19)30119-0], 2 Rehmann B, Thimme R. Insights From Antiviral Therapy into Immune Responses to Hepatitis B and C Virus Infection. Gastroenterology. 2019; 156: 369-383. [PMID: 30267712 DOI: 10.1053/j.gastro.2018.08.061]", please recheck again.

**Comment:**

Ok, following your suggestion, I rearranged the reference format.