June, 22nd 2021

Editorial board: World Journal of Hepatology

Dear Professors Ke-Qin Hu, Koo Jeong Kang and Nikolaos Pyrsopoulos – Editors-in-Chief

I am herewith submitting the revised manuscript entitled: "**Direct-acting antivirals for chronic hepatitis C treatment: the experience of two tertiary university centers in Brazil**" for appreciation of the World Journal of Hepatology Editorial Board, from authors Mariana Sandoval Lourenço, Patricia Momoyo Y. Zitelli, Marlone Cunha-Silva, Arthur Ivan N. Oliveira, Claudia P. Oliveira, Tiago Sevá-Pereira, Flair J. Carrilho, Mario G. Pessoa and Daniel F. Mazo.

We are grateful to the reviewers for the helpful comments on the original version of our manuscript. We have taken all the comments into account in order to resubmit this revised version with improvements.

Please find our answers to all the queries below.

The manuscript was previously sent to copyediting service by a professional English language editing company (American Manuscript Editors), (certificate attached).

We hope the revised version of our paper might now be suitable for publication in World Journal of Hepatology and we look forward to hearing from you at your earliest convenience.

Thank you in advance,

Daniel Ferraz de Campos Mazo, MD, PhD
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Reviewers' comments:

Reviewer #1:

Questions / comments:

1- I find the study interesting and with an adequate number of patients.

Response: Thank you.

Reviewer #2:

Questions / comments:

1- It is an interesting a Review about "Direct-acting antivirals for chronic hepatitis C treatment: the experience of two tertiary university centers in Brasil". My concern is determined in the following points. Sofosbuvir (SOF) plus Peginterferon and Ribavirin (PR) for 12 weeks needs to be considered as a treatment option for patients infected with HCV genotype 3. The currently approved regimen in the United States for the treatment of HCV genotype 3 infection is a 24-week regimen of SOF and weight-based doses of RBV. DAAs control HCV replication by at least two distinct mechanisms: (1) the direct inhibition of viral replication by antagonizing the function of viral proteins, and (2) the restoration of the endogenous IFN system via the robust introduction of ISGs. Therapeutic IFNs may maintain their position upon the emergence of difficult-to-treat HCV that is resistant to DAAs. In patients infected with HCV genotype 1, SOF may be used in combination with PEG-IFN/RBV, RBV alone, ledipasvir (LDV), or LDV and RBV. The combination of elbasvir and grazoprevir, with or without RBV, was highly efficacious in inducing an SVR12 in patients with HCV genotype 1, 4, or 6 infection. The retreatment of patients, who previously did not respond to DAAs therapies, with SOF-velpatasvir or/and plus RBV for 24 weeks was tolerated well and effective, particularly among those infected with HCV genotype 1 or 2. The combination of Glecavir and Pibrentasvir was highly efficacious and well tolerated in patients with HCV genotype 1 and genotype 2 infection, and prior failure of DAA-containing therapy. Treatments with drug combinations are sufficient to ultimately control the emergence of resistance-associated substitutions (RAS) in HCV. IFNs may play a role in the treatment of patients with DAA resistance and enhance the success of retreatment with DAA. A high rate of patients with genotype 3 HCV infection and compensated cirrhosis achieved an SVR with SOF and Velpatasvir without RBV. SOF/VEL therapy was effective and safe for patients with decompensated cirrhosis. Above mentioned should be referred to.

Response: Information regarding these topics was added in the Discussion section of the manuscript, as suggested by the reviewer.