ANSWERING REVIEWERS

February 18, 2014

Dear Editor,

we agree with your decision to publish, if accepted, this paper as "brief article".
Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript NO: 8841-edited).

Title: *IL28B* polymorphisms genotyping as predictor of rapid virologic response during Interferon plus ribavirin treatment in HCV genotype-1 patients.

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8841

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer No. 00012386

The study deals with a cohort of HCV genotype-1 infected patients who underwent dual therapy (Peg-interferon plus Ribavirin) without addition of direct antiviral agents (DDAs). Hence, the rate of side effects was similar to that reported by literature. In Italy 1st generation antivirals such as telaprevir or boceprevir entered clinical practice only in 2013.

(2) Reviewer No. 02528622

Our work aims at emphasizing the role of the *IL28B* polymorphisms genotyping in HCV genotype-1 patients for which triple therapy is not suited. In these patients the evaluation of pre-treatment factors such as the *IL28B* SNPs still hold significance to establish the therapeutic schedule. The study cohort is described in table 1 which includes genotypes of patients who did not achieve rapid virological response and overall treatment outcome. The Non responder (NR) group (n = 65) includes 26 Null-R, 34 Par-R and 5 Relapser.

(3) Reviewer No. 00504486

According to the reviewer suggestion we removed from the title "Potential clinical implications at the time of triple therapy". We agree that this sentence could lead to misinterpretation of our results. All indicated typos were corrected.

(4) Reviewer No. 02861401

Indeed Hepatitis C Virus therapy is currently undergoing a very rapid transformation with the advent of 2nd and 3rd generation of Direct Antiviral Agents. Nevertheless this is happening in a very heterogeneous way: while in US triple therapy is the standard of care treatment for HCV G1 infected patients since 3 years, this is not the case for many European and other countries, where dual therapy

remains the available therapeutic treatment .

As reported in the discussion section, *IL28B* genotyping for both SNPs together with other baseline features (viremia, fibrosis staging) and RVR assessment are criteria for addressing patients to dual versus triple therapy regimens. This is also well stated in the paper by Andriulli et al. ref.22.

IFN-free therapy is expected to become the standard of care soon and it is especially required in IFN-resistant patients. For these reasons, we emphasize the use of IL28B SNPs to help clinicians to select IFN sensitive subjects. In a recent review, Matsuura and colleagues (ref.30), reported that the *IL28B* polymorphisms may affect viral kinetics even in the context of IFN-free regimens. Moreover, they reported that in a phase 2b, randomized, open-label trial of faldaprevir (NS3/4A protease inhibitor) and deleobuvir (NS5B polymerase inhibitor), the SVR rates tended to be higher in patients with CC at rs12979860 than in those with non-CC. This suggests that innate immunity may still be important and IL28B genotype may affect treatment efficacy in certain IFN-free regimens..

Statistical analysis: to identify predictors of Null-R we performed a stepwise logistic regression analysis in which the *IL28B* SNPs were evaluated according to the presence of the risk allele versus favorable homozygosis. The aim of our study was not to identify the good responders to Peg-IFN plus RBV therapy. We focused on the HCV viremia drop at treatment week 4 to select IFN sensitive patients. We explored the interaction between the *IL28B* rs12979860 and rs8099917 SNPs (see Table 3 in the manuscript). We analyzed HCV RNA kinetic during 12 weeks of therapy in carriers of the *IL28B* rs12979860 CT heterozygosis according to their rs8099917 status to empathize the weight of the rs8099917 G allele carriage despite the presence of the favorable rs12979860 C allele. In fact the rs12979860 CT heterozygosis group has a high frequency in the population.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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