

**ESPS Peer-review Report**
**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 8841

**Title:** IL28B polymorphisms genotyping as predictor of rapid virologic response during Interferon plus ribavirin treatment in HCV genotype-1 patients. Potential clinical implications at the time of triple therapy

**Reviewer code:** 00012386

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2014-01-11 17:24

**Date reviewed:** 2014-01-11 21:52

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

**COMMENTS TO AUTHORS**

Rosso et al. reported that IL28B genotype was rs8099917 (G\*)/rs1297860(\*\*) in 21/26 (80%) of null-Responder patients after the treatment with telaprevir-including triple therapies. This article may provide important information in this area. 1. How about the adherence to drugs (peginterferon/ribavirin/teraprevir/duration)? Authors should show and analyze them. Because these are important factors of treatment response. 2. In Introduction section, Authors mentioned that "....but raises concerns regarding the development of resistant viral variants and significant side effects[7]....." How about the side-effects in authors' patients? How about the adherence of drugs in the patients with side effects? Authors should clearly show the adverse events and whether there was an association between adverse events and treatment response. 3. Authors should show the SVR rates. This is one major problem.

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**Title:** IL28B polymorphisms genotyping as predictor of rapid virologic response during Interferon plus ribavirin treatment in HCV genotype-1 patients. Potential clinical implications at the time of triple therapy

**Reviewer code:** 02528622

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2014-01-11 17:24

**Date reviewed:** 2014-01-15 11:22

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

# COMMENTS TO AUTHORS

This study addresses an issue that has been analyzed in detail in numerous reports in the literature. As mentioned by the reviewers, a immense number of papers were published following the report by Ge et al in 2009. However, the importance of IL28B genotype in therapy outcome has been reduced significantly with the arrival of new DAAs. The recent approval of sofosbuvir, and the imminent arrival of several powerful DAAs is likely to result in the elimination of IFN from the anti-HCV therapy regime, further reducing the need for IL28B genotyping in the new IFN free era. This study comes after nearly three years of DAA therapy and couple of months after the approval of the first HCV polymerase inhibitor. In a rapidly evolving landscape for anti-HCV drugs, this papers lacks novelty and does not bring new information to the field. Additionally, the authors do not describe the full picture for this cohort. The authors should present the data from so called partial-responders and relapser as well as rapid responder and SVR cases. The authors only present data regarding heterozygous cases. The data for cases exhibiting homologous alleles should also be presented and discussed in the paper. While approval of the current DAAs in several regions of the world has hampered our ability to treat HCV infected cases, the health problem at hand is of a political/administrative nature. Likewise, cost of therapy limits the benefits of the current STAT-C. All these factors, however, do not justify the data presented in this paper. As mentioned above, the body of information regarding use of IL28B genotyping has been shown repeatedly, and confirmed a number of times.

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**ESPS Manuscript NO:** 8841

**Title:** IL28B polymorphisms genotyping as predictor of rapid virologic response during Interferon plus ribavirin treatment in HCV genotype-1 patients. Potential clinical implications at the time of triple therapy

**Reviewer code:** 00504486

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2014-01-11 17:24

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> [ Y] Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> [ ] Existed	<input type="checkbox"/> [ ] High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> [ ] No records	<input type="checkbox"/> [ ] Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> BPG Search:	<input type="checkbox"/> [ ] Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> [ ] Existed	<input type="checkbox"/> [ ] Major revision
		<input type="checkbox"/> [ ] No records	

# COMMENTS TO AUTHORS

This study has shown that IL28B SNP can determine the effectiveness of pegylated-IFN and ribavirin (PEG-IFN/RBV) treatment in HCV genotype 1 patients. In the study, patients carrying both IL28B rs 12979860 CT and rs 8099917 TT show more sensitive to PEG-IFN/RBV than patients carrying IL28B rs 12979860 CT and other SNPs. Furthermore, the study reports that IL28B rs8099917G allele possesses resistance to PEG-IFN/RBV. Accordingly the authors propose that genotyping of both IL28B SNPs is useful in clinical practice for patient risk stratification based on IFN responsiveness. We think their results of IL28B SNP are clear and significant for clinical treatment of HCV genotype 1 patients. Although the authors mentioned risks and side effects of triple therapy including IFN, ribavirin and protease inhibitor, they did not include triple therapy for the treatment of HCV genotype 1 patients. Since they did not include triple therapy in this experiment setting, we suggest removal of "Potential clinical implications at the time of triple therapy" in title. Otherwise, this sentence makes confusion and dilution of their findings; importance of IL28B SNP for IFN/Ribavirin treatment. We found some typo errors. 1. In Result part, first page line15; at 12 week.. -> at 12 week. 2. In Discussion part, 3rd page line 3 ; IL 28B SNP-> IL 28B SNP.

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**ESPS Manuscript NO:** 8841

**Title:** IL28B polymorphisms genotyping as predictor of rapid virologic response during Interferon plus ribavirin treatment in HCV genotype-1 patients. Potential clinical implications at the time of triple therapy

**Reviewer code:** 02861401

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2014-01-11 17:24

**Date reviewed:** 2014-01-21 21:46

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
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<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

Lacking of novelty is the major issue of this article. The article once again confirmed the association of IL28B genotypes (both rs12979860 C/T and rs8099917 T/G) with genotype 1 HCV response when patients were treated with Peg-IFN/RBV (P/R). Although this is very important information, it has been addressed in numerous peer-reviewed articles and telaprevir/boceprevir labels (at least for rs12979860 C/T). Although the authors claimed they were going to identify the patients could still be benefited from the dual therapy as their aim, their work did not adequately serve their purpose. They don't have clear criteria for patients could still be benefited from the dual therapy. These criteria are very important and should be clearly specified especially when the HCV treatment is currently under a very rapid change. Even for areas where DAAs are currently not widely available, current consideration is to do delay the treatment instead of the P/R treatment. New DAAs (e.g., sofosbuvir and simeprevir) largely decrease the duration of treatment and are generally well-tolerant. Those factors were not fully discussed in the article. The statistical analyses lack of details and important information (e.g., the model of multivariate analysis were not clearly defined and the results are not clearly explained) and the analyses did not serve their purpose to identify the good responders to P/R (for this purpose they should use some variable like RVR instead of Null-R). The analyses did not adequately explore the interaction between rs12979860 C/T and rs8099917 T/G either.