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Polymorphisms of *IFNL3* and Response to Interferon-Based Treatments in Patients with Hepatitis D Infection: Systematic Review and Meta-Analysis

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To the Editor,

The hepatitis D virus (HDV) is a RNA virus that needs the hepatitis B virus (HBV) surface antigen (HBsAg) to complete its life cycle (1). HDV has a worldwide distribution; the infection is endemic in the Middle East, Mediterranean countries, Central Africa, and northern parts of South America (2). Clinical outcomes vary from asymptomatic to fulminant hepatitis; although, HDV is usually related to a severe form of hepatitis (2). HDV has no specific functional enzyme to be targeted for therapy, therefore, using Interferon (IFN)-based treatments are the only available treatment for a chronic HDV infection with low efficacy around 10% - 40% (3, 4). Previously, it was found that polymorphisms near *IFNL3 (IL28B)* modify the rate of response to IFN-based treatments in patients with the hepatitis C infection (5). It is of great interest to observe whether the same is true in patients with the HDV infection who were treated with IFN-based treatments (6-10). This short systematic review and meta-analysis aimed to evaluate the impact of polymorphisms near *IFNL3* (rs12979860 and rs8099917) on sustained virologic response (SVR) in patients with the HDV infection who were treated with IFN-based treatments.

In this study, we searched PubMed, Scopus, and Web of Science for the relevant articles with the following keywords: "HDV", "Hepatitis D", "IL28B", and "*IFNL3*" (Search date: 25 August, 2016). The search results were screened for appropriate titles and abstracts. Finally, full-texts were evaluated for inclusion of the studies in the meta-analysis. The Peto method was used for pooling the data. Data analysis was performed using Review Manager 5.3 (Cochrane Collaboration, London, UK).

The systematic search identified 42 articles while finally, 5 articles were included after exclusion of duplicates and screening of titles, abstracts, and full-texts. The data of the included studies are presented in Table 1. All of the 5 included studies assessed the rs12979860 polymorphism, including a total of 246 patients with the HDV infection who were treated with IFN-based treatments. Based on the forest plot in Figure 1A, the rate of SVR to IFN-based treatments was slightly lower in HDV patients with rs12979860 CC than in those with rs12979860 non-CC genotypes (26.4% vs. 37.5%) (P = 0.05; OR = 0.57; 95%CI = 0.33-1.01). Moreover, 3 studies including a total of 96 patients with the HDV infection were available with the data of impact of rs8099917 polymorphism on SVR rate to IFN-based treatments. As shown in Figure 1B, the SVR rate was not significantly different between HDV patients with rs8099917 TT and non-TT genotypes treated with IFN-based treatments (40.7% vs. 45.9%) (P = 0.75; OR = 0.87; 95%CI = 0.38 - 2.03).

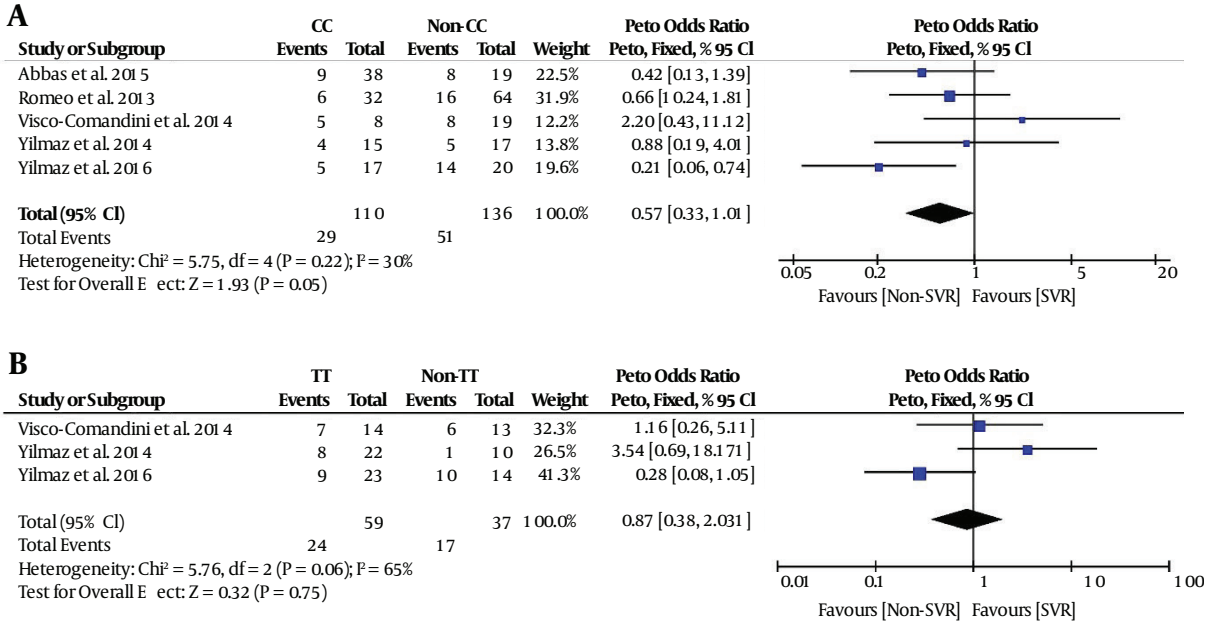
While the studies on patients with HCV infection showed that rs12979860 CC genotype is associated with a favorable response to IFN-based treatment (5), the current meta-analysis showed that rs12979860 CC might be associated with a lower response rate to IFN-based treatments in patients with HDV infection than those with rs12979860 non-CC genotype treated with IFN-based treatments. If we accept that this polymorphism acts inversely in treatment of the HDV infection to that of the HCV treatment, then it is very interesting to find out the mechanism in which rs12979860 polymorphism modify the treatment response in HDV patients. Furthermore, this meta-analysis found no association between rs8099917 polymorphism and SVR rate to IFN-based treatments in patients with the HDV infection. Unfortunately, the number of studies of the impact of *IFNL3* polymorphisms on SVR to IFN-based treatments in HDV patients is limited; therefore, there is great need for more studies in this field for clarification of the

Table 1. The Characteristics of the Included Studies

Study	Publication Year	Country	Sample Size, n	Male, %	Age, Year (Mean or Median)	Cirrhosis, %	rs12979860, CC/non-CC,%	rs8099917, TT/non-TT,%	Treatment Regimen	Treatment Duration, mo	SVR, %
Abbas et al.	2015	Pakistan	57	82.8	30.5	43.8	66.7/33.3	NA	pegIFN	12	29.8
Romeo et al.	2013	Italy	93	68.4	56	NA	34.4/65.6	NA	sIFN	6 - 94	23.7
Visco-Comandini et al.	2014	Italy	27	70.9	50	55.6	29.6/70.4	51.9/48.1	pegIFN or sIFN	4 - 36	48.1
Yilmaz et al.	2016	Turkey	37	56.8	41	35.1	45.9/54.1	62.2/37.8	pegIFN	12 - 30	51.4
Yilmaz et al.	2014	Turkey	32	59.4	42.5	18.8	46.9/53.1	68.8/31.2	pegIFN or sIFN	12 - 30	28.1

Abbreviations: NA, not available; pegIFN, Pegylated interferon; sIFN, standard interferon; SVR, sustained virologic response.

Figure 1. The Impact of *IFNL3* Polymorphisms on Sustained Virologic Response (SVR) in HDV Patients Treated with IFN-Based Treatments



A, rs12979860 and SVR to IFN-based treatments in HDV patients; B, rs8099917 and SVR to IFN-based treatments in HDV patients.

role of host genetics on treatment success of HDV infection.

Footnotes

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