Correspondence

Reply: Subgroup Differences in Response to 8 Weeks of Ledipasvir/Sofosbuvir for Chronic Hepatitis C

To the Editor—We congratulate Dr. Kowdley and his colleagues [1] on their very important paper demonstrating high sustained virological response (SVR) rates among treatment-naive patients without cirrhosis who received ledipasvir/sofosbuvir for 8 weeks in the ION-3 trial. We also thank them for their interest in our reanalysis of those published data in which we demonstrated that response in ION-3 differed significantly by both gender and rs12979860 ("IL28B") genotype, with SVR rates exceeding 98% in women and individuals with the rs12979860-CC genotype [2]. The very high SVR rates in these 2 subgroups suggested to us that these factors might be considered in selecting patients to receive 8 weeks of ledipasvir/sofosbuvir. In their letter, Kowdley et al [3] present data for SVR by gender and rs12979860 genotype additionally stratified by the pretreatment hepatitis C virus (HCV) RNA level categories of <6 million IU/mL or ≥6 million IU/mL. An HCV RNA measurement of <6 million IU/mL is the basis for current prescribing guidance for considering a patient for 8-week treatment with ledipasvir/sofosbuvir.

Using these data, which were not available from the original paper [1], we combined subjects from the 2 8-week treatment arms (with or without ribavirin) and again calculated SVR rates separately by genotype and by gender, now stratifying by the pretreatment HCV RNA level (Table 1). In the analysis of host genotype, the SVR rate was 100% among patients with the favorable rs12979860-CC genotype and an HCV RNA <6 million IU/mL. Very high SVR rates were also seen in patients who had a favorable genotype, but a high viral level (96%), as well as in patients who combined an unfavorable genotype with a low viral level (97%). The SVR rate was 89% among patients in whom both the genotype and the viral level were unfavorable. A virtually identical pattern was seen when we examined SVR rates by gender and stratified by HCV RNA, with an SVR rate of 96% in women with an HCV RNA level ≥6 million IU/mL (Table 1). These results indicate that even after HCV RNA is considered, host genotype and gender are informative for predicting SVR in response to treatment with ledipasvir/sofosbuvir for 8 weeks, and that certain patients in the high viral level group have a very high likelihood of responding to this shorter regimen.

We fully agree with Kowdley et al [1] that "real world" data for large numbers of patients are needed to inform decisions for treatment of patients with ledipasvir/sofosbuvir for 8 weeks. Such data might be used to examine the current assumption that an HCV RNA cutoff of <6 million IU/mL, which is based solely on data obtained from ION-3, is the best treatment threshold. However, the optimal approach for utilizing such data for treatment decisions would also require developing and validating clinical prediction models based on all relevant individual patient characteristics. Stratification of patients based on individual predictions of SVR could lead to cost-effective and efficient "precision medicine" for the treatment of chronic hepatitis C.

Table 1. Rates of SVR in Patients Receiving Ledipasvir/Sofosbuvir or Ledipasvir/Sofosbuvir/Ribavirin for 8 Weeks, by Population Subgroup and HCV RNA Level, ION-3

	HCV RNA Level					
	<6 million IU/mL			≥6 million IU/mL		
	SVR	Total	SVR Rate	SVR	Total	SVR Rate
rs12979860						
CC	66	66	100%	45	47	96%
CT/TT	186	191	97%	106	119	89%
Sex						
Female	126	126	100%	52	54	96%
Male	126	131	96%	99	112	88%

Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response.

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Thomas R. O'Brien[1] and Ruth M. Pfeiffer[2]

[1]Infections and Immunoepidemiology Branch, and [2]Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

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Correspondence: Thomas R. O'Brien, MD, MPH, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Dr, 6E108, MSC 9767, Bethesda, MD 20892 (obrient@mail.nih.gov).

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