Correspondence

Analysis of Subgroup Differences in the ION-3 Trial of Ledipasvir-Sofosbuvir in Chronic Hepatitis C Infection

To the Editor—We read with interest the Brief Report by Dr. O'Brien and colleagues [1] of an analysis of subgroup differences in the ION-3 trial, which evaluated 8 and 12 weeks of ledipasvir-sofosbuvir in treatment-naive patients with genotype 1 hepatitis C virus (HCV).

The authors note that the prescribing instructions for ledipasvir-sofosbuvir state that shortening treatment duration from 12 to 8 weeks should be considered in patients with baseline HCV RNA <6 million IU/mL [2]. This recommendation was based on the observation that among ION-3 patients with baseline HCV RNA <6 million IU/mL, relapse rates were similar among those receiving 8 weeks of treatment and those receiving 12 weeks of treatment. O'Brien and colleagues [1] hypothesize that consideration of subgroup differences in addition to viral load may help more accurately identify patients who may be treated for 8 weeks without compromise of efficacy. They suggest that our modified intent-to-treat analysis, which counted patients with missing posttreatment week 12 results as treatment failures, may mask differences in response among patient subgroups.

Using subgroup data from ION-3, they performed a per-protocol analysis, excluding patients who were lost to follow-up or withdrew consent. This analysis identified 2 factors with a statistically significant association with sustained virological response 12 weeks (SVR12): female gender and the CC genotype of IL28B (rs12979860). They propose that consideration of these factors may help clinicians more accurately identify patients who can be treated for 8 weeks than baseline viral load alone.

To evaluate their hypothesis, we analyzed SVR12 rates by gender, IL28B genotype, and baseline HCV RNA in the per-protocol population (those who were lost to follow-up or withdrew consent were excluded from both the denominator and numerator). The analysis includes 2 patients in the 12-week group who were counted as failures in the original report because they were lost to follow-up at posttreatment week 12 but were subsequently found to have SVR at a posttreatment week 24 visit.

Table 1 shows that among patients with baseline HCV RNA <6 million IU/mL, those who received 8 weeks of treatment had SVR rates similar to those who received 12 weeks of treatment, and that SVR rates did not differ in this group of patients on the basis of gender or IL28B genotype.

This analysis indicates that an HCV RNA threshold of <6 million IU/mL is sufficient to identify patients who can receive 8 weeks of treatment without loss of efficacy; gender and/or IL28B status do not add value with regard to selecting treatment duration beyond that offered by baseline viral load.

Nevertheless, it is recognized that, especially given the few number of failures overall, post hoc analysis is not a substitute for real-world data derived from thousands of patients, which will ultimately determine the patient subpopulation in whom 8 weeks of treatment is the optimal duration.

Table 1. SVR12 Rates by Gender, IL28B Genotype, and Baseline HCV RNA in the Per-Protocol Population

	LDV/SOF 8 wks	LDV/SOF + RBV 8 wks	LDV/SOF 12 wks
All Patients			
IL28 CC	54/56 (96%)	57/57 (100%)	54/54 (100%)
IL28 CT	112/119 (94%)	120/125 (96%)	120/122 (98%)
IL28 TT	36/38 (95%)	24/28 (86%)	34/35 (97%)
Male	119/129 (92%)	106/114 (93%)	124/127 (98%)
Female	83/84 (99%)	95/96 (99%)	84/84 (100%)
Patients With Baseline HCV RNA <6 000 000 IU/mL			
IL28 CC	30/30 (100%)	36/36 (100%)	31/31 (100%)
IL28 CT	63/65 (97%)	78/80 (98%)	72/73 (99%)
IL28 TT	26/26 (100%)	19/20 (95%)	23/24 (96%)
Male	64/66 (97%)	62/65 (95%)	72/74 (97%)
Female	55/55 (100%)	71/71 (100%)	54/54 (100%)
Patients With Baseline HCV RNA ≥6 000 000 IU/mL			
IL28 CC	24/26 (92%)	21/21 (100%)	23/23 (100%)
IL28 CT	49/54 (91%)	42/45 (93%)	48/49 (98%)
IL28 TT	10/12 (83%)	5/8 (63%)	11/11 (100%)
Male	55/63 (87%)	44/49 (90%)	52/53 (98%)
Female	28/29 (97%)	24/25 (96%)	30/30 (100%)

Abbreviations: HCV, hepatits C virus; LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; SVR12, sustained viral response 12 weeks.

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