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

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Treatment of hepatitis C virus (HCV) infection with ledipasvir/sofosbuvir promises tremendous benefits, but high cost may impede implementation of this regimen. Subgroups with excellent response to 8 weeks of treatment might respond to a shorter course. In ION-3, 423 previously untreated HCV genotype 1-infected patients without cirrhosis had outcome data after receiving ledipasvir/sofosbuvir for 8 weeks. After reanalyzing published ION-3 data, we found that sustained virologic response (SVR) rates varied significantly by gender ($P = .002$) and rs12979860 genotype ($P_{trend} = .03$), exceeding 98% in women and rs12979860-CC individuals. The very high SVR rates in these subgroups suggest that these factors might be considered in selecting patients to receive 8 weeks of ledipasvir/sofosbuvir and support shorter trials of this regimen in selected patients.

Keywords. clinical trial; cost-effectiveness; direct-acting antiviral agents; gender; hepatitis C virus; *IFNL4*.

New "interferon-free" regimens based on direct-acting antiviral agents (DAAs) against hepatitis C virus (HCV) promise tremendous benefits, but high costs may impede their implementation [1, 2]. Shortening treatment duration could reduce those costs, as well as associated adverse effects. Ledipasvir/sofosbuvir has recently been licensed by the US Food and Drug Administration; initial prescribing guidance for this regimen is that treatment for 8 weeks can be considered in treatment-naive patients without cirrhosis who have pretreatment HCV RNA <6 million IU/mL. Evidence of population subgroup differences in treatment response to 8 weeks of treatment with ledipasvir/sofosbuvir might be used to improve these recommendations and to identify patients who are likely to respond to an even shorter course of treatment.

An analysis of the ION-3 trial of 8 or 12 weeks of treatment with ledipasvir/sofosbuvir that counted patients as treatment failures if they were lost to follow up or withdrew from the trial (as often done in an intention-to-treat analysis) found no subgroup differences [1]. Designating individuals with missing outcome data as "treatment failures" provides a conservative assessment of the comparative effectiveness of competing regimens; however, for highly effective therapies, this practice may impede detection of differences in response among patient subgroups. In ION-3, overall response to 8 or 12 weeks of ledipasvir/sofosbuvir exceeded 90%, and, as a result, enrollees with missing outcome data constituted 39% of those counted as treatment failures [1]. In this situation, an "efficacy" analysis restricted to patients with outcome data may be more informative to identify subgroup differences. Therefore, we performed a subgroup analysis of published data from ION-3 that excluded individuals with missing outcome data.

METHODS

ION-3 enrolled previously untreated patients with chronic HCV genotype 1 infection without cirrhosis. Participants were randomized to receive ledipasvir (90 mg)/sofosbuvir (400 mg) for 8 weeks, ledipasvir/sofosbuvir plus ribavirin for 8 weeks, or ledipasvir/sofosbuvir for 12 weeks [1]. Published supplemental information included subgroup-specific counts for sustained virologic response (SVR) 12 weeks after the end of treatment (Supplementary Table 2) [1]. These subgroups (and categories) included: age (<65 or ≥65), sex, race (Black or Non-black), ethnicity (Hispanic or Non-Hispanic), HCV genotype (1a or 1b); rs12979860 genotype. Subgroup information for the 23 patients who suffered virologic relapse after the end of therapy was also published (Supplementary Table 4) [1]. No patient suffered a viral breakthrough while under treatment, and only 3 subjects (1 in an 8-week arm and 2 in the 12-week arm) discontinued treatment prematurely due to adverse events.

We calculated SVR rates by dividing the number of subjects who achieved SVR by the sum of patients with known treatment outcome (ie, virologic relapse or SVR). Our primary analysis combined subjects from the two 8-week treatment arms (with or without ribavirin), because those data are most relevant to whether treatment for <8 weeks might be effective in some subgroups. We also conducted an analysis of all 3 arms combined

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(the 12-week treatment arm and the two 8-week arms). *P* values were calculated by Fisher's exact test or an exact test for trend.

RESULTS

Among the 431 individuals assigned to receive 8 weeks of ledipasvir/sofosbuvir, 428 completed treatment and 423 had outcome data, thus 5 of the 8 subjects without outcome data had completed treatment. Among patients with outcome data, 403 (95.3%) achieved SVR (Table 1). SVR rates exceeded 90% in all subgroups examined, yet varied significantly by gender ($P = .002$) and rs12979860 ("IL28B") genotype ($P_{trend} = .03$). Black patients had a lower SVR rate than individuals of other racial groups; however, that association did not reach statistical significance ($P = .08$). The SVR rate was 98.9% in women and 98.2% in individuals with the rs12979860-CC genotype, who together constituted >50% of study participants.

The 3 arms of ION-3 combined included 647 individuals who were assigned to receive treatment, 639 of whom completed treatment and 632 of whom provided outcome data. The analysis combining all 3 arms of ION-3 (Table 1) yielded smaller *P* values for gender ($P = .0008$), rs12979860 genotype ($P_{trend} = .02$), and race ($P = .03$).

DISCUSSION

In contrast to the original report, our analysis reveals statistically significant differences in treatment response among patient subgroups in ION-3. This discrepancy reflects different approaches to missing outcome data. No consensus exists on the best method for dealing with missing data in clinical trials [3, 4], and alternative approaches are based on different assumptions [4]. The original analysis assumes the worst-case scenario—all patients with missing outcomes failed treatment, including those who completed the highly effective ledipasvir/sofosbuvir regimen. Our analysis assumes individuals with missing outcomes and patients who completed the protocol would have achieved similar response rates if the former group had completed the protocol. In this case, it appears that treating individuals with missing data as treatment failures, combined with the modest statistical power in ION-3 for subgroup analyses, obscured true differences in treatment outcome among subgroups.

The finding that women are more likely to clear HCV infection after treatment with ledipasvir/sofosbuvir is consistent with results from a previous trial of a DAA-based regimen [5], and women are also more likely to clear HCV spontaneously [6]. It is not clear why women clear HCV more readily than men; however, hormonal factors are implicated by reports that

Table 1. Rates of SVR in Patients Receiving Ledipasvir/Sofosbuvir or Ledipasvir/Sofosbuvir/Ribavirin for 8 Weeks or 12 Weeks, by Population Subgroup, ION-3

	8 Weeks					8 or 12 Weeks				
	SVR	Relapse	Total	SVR Rate	*P* Value	SVR	Relapse	Total	SVR Rate	*P* Value
Overall	403	20	423	95.3%		609	23	632	96.4%	
Age										
<65	374	17	391	95.7%		563	20	583	96.6%	
≥65	29	3	32	90.6%	.2	46	3	49	93.9%	.4
Sex										
Male	225	18	243	92.6%		347	21	368	94.3%	
Female	178	2	180	98.9%	.002	262	2	264	99.2%	.0008
Race										
Black	73	7	80	91.3%		113	9	122	92.6%	
Non-black	330	13	343	96.2%	.08	495	14	509	97.2%	.03
Ethnicity										
Hispanic	25	0	25	100%		38	1	39	97.4%	
Non-Hispanic	376	20	396	94.9%	.6	569	22	591	96.3%	1.0
HCV genotype										
1a	318	17	335	94.9%		481	19	500	96.2%	
1b	84	3	87	96.6%	.8	127	4	131	96.9%	.8
rs12979860 genotype										
CC	111	2	113	98.2%		165	2	167	98.8%	
CT	232	12	244	95.1%		350	14	364	96.2%	
TT	60	6	66	90.9%	.03*	94	7	101	93.1%	.02*

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

* Trend test; missing data (all in patients with SVR): race (n = 1), ethnicity (n = 2), HCV genotype (n = 1).

postmenopausal women achieve SVR less frequently than women of reproductive age (but as frequently as men) [7]. Associations between interferon-λ region genetic variants and response to interferon-free DAA regimens have also been observed previously [5, 8] and are consistent with results from studies of spontaneous HCV clearance [9, 10]. The functional mechanism by which genetic variation in this region impairs viral clearance remains under investigation [11], but our analysis provides additional evidence that the association is not restricted to response to treatment with interferon-α-based regimens.

This analysis of published data has important limitations. Available data did not provide the individual level information that would be needed to assess confounding relationships or to substratify the analysis. For example, the finding that black patients responded to ledipasvir/sofosbuvir treatment less often than other patients is likely confounded by host genotype, because people of African ancestry carry favorable interferon-λ region alleles less frequently than those of European ancestry, and previous studies have shown that most or all of the association of "race" with treatment response is explained by these differences in allele frequency [9, 12]. With regard to substratification, the age of female patients may be relevant because some studies of interferon-α-based regimens reported lower efficacy rates in postmenopausal women [7]. However, only 2 women in this analysis failed to respond to treatment, precluding meaningful analysis of any subgroups in females, even if individual-level data were available. Another limitation is that host genotype information for this study was based on the rs12979860 variant; genotype for the *IFNL4*-ΔG/TT (rs368234815, previously designated ss469415590) variant is a better predictor of HCV clearance, especially in individuals of African ancestry [9]. Of note, 1 of the 2 patients with the rs12979860-CC genotype who completed treatment yet failed to achieve SVR was an African American male, and we speculate that this patient may have had an unfavorable *IFNL4*-ΔG/TT genotype.

Our finding that 8 weeks of treatment with ledipasvir/sofosbuvir led to SVR rates of 98%–99% in women and individuals with a favorable interferon-λ genotype suggests that these factors might be useful for identifying patients who are most likely to respond to 8 weeks of treatment. The initial guidance suggests that 8 weeks for treatment be restricted to patients with a pretreatment HCV RNA <6 million IU/mL. Previous studies have shown that the prognostically favorable rs12979860-CC genotype is, paradoxically, also associated with higher HCV RNA levels [12]. Given this complex relationship, the current recommendation based on HCV RNA alone may be too restrictive, and consideration of both host genotype and HCV RNA levels might be required to identify patients who are most likely to respond to shorter durations of treatment.

Our findings support the concept of shorter trials of this regimen in selected individuals. The minimal length of treatment with this regimen that might achieve SVR is unknown; however, a woman with a favorable genotype for the *IFNL4*-ΔG/TT variant attained SVR after 27 days of treatment with sofosbuvir and ribavirin, a less potent regimen than ledipasvir/sofosbuvir [13]. Gane et al [14] treated 25 patients with ledipasvir/sofosbuvir plus ribavirin for 6 weeks and found that 17 (68%) achieved SVR; however, subgroup results were not reported for that small trial. Trials of ledipasvir/sofosbuvir have demonstrated efficacy >90% for treatment durations ranging from 8 to 24 weeks. The evidence that response to this regimen varies by population subgroup suggests these factors might help determine the optimal duration of therapy for individual patients.

Decreasing the course of therapy with ledipasvir/sofosbuvir could yield substantial healthcare cost savings. Women and individuals with the rs12979860-CC genotype (the subgroups responding best to 8 weeks of treatment) constituted over half of subjects in ION-3, a study population that was nationally representative for the United States [1]. In this country, ~3 million individuals are chronically infected with HCV [15]. Assuming that the cost of treatment with ledipasvir/sofosbuvir will be $1125/day, for every 100 000 patients who could be treated for 2 fewer weeks (eg, 6 weeks rather than 8 weeks), cost savings of >$1.5 billion dollars might be achieved.

Supplementary Material

Supplementary material is available online at *Open Forum Infectious Diseases* (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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