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No Scientific Basis to Restrict 8 Weeks of Treatment with Ledipasvir/Sofosbuvir to Patients with HCV RNA <6,000,000 IU/ml

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In an important paper, Kowdley and colleagues demonstrated a sustained virological response (SVR) rate of 93.5% in an intention-to-treat analysis among hepatitis C virus (HCV) genotype 1-infected treatment-naïve patients without cirrhosis who received ledipasvir/sofosbuvir for 8 weeks in the ION-3 trial.(1) Furthermore, the authors found treatment for 8 weeks to be non-inferior to 12 weeks of treatment with this regimen.(1) A subsequent efficacy analysis that excluded the patients who did not complete the study (most of whom had completed the full course of treatment) produced an even higher SVR rate (95.3%) in patients treated for eight weeks.(2) From a population perspective, these findings are notable because individuals meeting the eligibility criteria for ION-3 (HCV genotype 1 infection without cirrhosis or prior HCV treatment) may represent the majority of HCV-infected individuals in the United States and many other countries.

Drug costs are a major barrier to implementing treatment for HCV with regimens based on direct-acting antiviral agents (DAAs)(3) and the current stated price for the daily ledipasvir/sofosbuvir fixed dose combination (trade name, Harvoni) in the United States is $1125/tablet. If many of the estimated 3.2 million people living with chronic hepatitis C in the United States could be treated for 8 weeks, the substantial resulting healthcare savings would allow treatment of many more patients for the same overall cost. The US label for Harvoni stipulates that 8 weeks of treatment should be considered only for patients with an

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HCV RNA <6,000,000 (6.78 $\log_{10}$) IU/ml, a level which, to our knowledge, has not been used previously for any treatment decisions. Given the importance of this criterion, we examined its statistical basis.

The 6,000,000 IU/ml level was selected after *post hoc* comparisons of virological relapse rates in the 8 and 12 week arms of the ION-3 trial conducted during the pre-licensure statistical review for ledipasvir/sofosbuvir.(4) Statistical interaction between the two 8 week arms combined (with or without ribavirin, n= 429) and the 12 week arm (n=216) of ION-3 was examined for 13 HCV RNA categories (Table 1). For subgroup analyses, an examination of relapse rates (or a 'per protocol' analysis of SVR) has greater statistical power (and other advantages) compared to an intention-to-treat analysis, however, statistical power for the interaction analyses of HCV RNA remained extraordinarily low due to the small number of patients who relapsed, most importantly only three in the 12 week arm. Based on the ION-3 data, we calculate that the power was only 5% to detect a statistically significant association ($p<0.05$) for a two-fold interaction between the 8 and 12 week arms (based on the 6,000,000 IU/ml threshold), and that >4000 subjects would have been required to provide adequate statistical power for assessing an effect of HCV RNA in that manner. Consequently, the likelihood of detecting a statistically significant association in that analysis was extremely small even without adjusting for the multiple statistical comparisons that were made. It is not surprising, therefore, that although the smallest of the 13 p-values was observed for the 6,000,000 IU/ml categorization, the p-value for that finding ($p=0.20$) did not approach even nominal statistical significance. Furthermore, much larger p-values were seen for the next lower (5,000,000 [6.70 $\log_{10}$] IU/ml, $p=1.0$) and next higher (7,000,000 [6.85 $\log_{10}$] IU/ml, $p=0.55$) HCV RNA cutoffs (Table 1), providing additional evidence that the p-value nadir observed for the 6,000,000 IU/ml threshold is likely a statistical artefact.

Introducing a finding without a strong statistical basis into the drug licensure process creates a dilemma for guideline committees and there is currently a range of recommendations regarding the duration of ledipasvir/sofosbuvir treatment for previously untreated HCV genotype 1-infected patients without cirrhosis. For the English National Health Service, the preliminary recommendation is 8 weeks of treatment for these patients, regardless of HCV RNA level (http://www.nice.org.uk/guidance/GID-TAG484/documents/hepatitis-c-chronic-ledipasvirsofosbuvir-id742-appraisal-consultation-document-12). EASL practice guidelines state, 'treatment may be shortened to 8 weeks … if their baseline HCV RNA level is below 6 million IU/ml', but 'this should be done with caution'.(5) Current AASLD/IDSA guidelines recommend a 12 week course for all such patients.(6)

While the severe limitations of the *post hoc* analysis of HCV RNA levels in ION-3 raise serious questions regarding the <6,000,000 IU/ml level as a criterion for shorter treatment, it is very plausible that valid and useful clinical prediction models for response to ledipasvir/sofosbuvir (and other DAA-based regimens) could be developed. Patient sex and *IFNL4* rs1297860 genotype have been associated with treatment response in ION-3, with all relapses occurring in either males or in women who had an unfavorable *IFNL4* genotype. (2) Liver fibrosis might also be relevant to treatment response, but that variable has not been evaluated carefully in the ION-3 dataset. Regarding viral factors, the presence of NS5A

resistance associated variants (RAVs) may predict response to regimens that include NS5A inhibitors such as ledipasvir. Pretreatment HCV RNA levels could inform clinical prediction algorithms for DAA-based treatment, however, that variable must be addressed with consideration of the sample size required for adequate statistical power, as well as some inherent limitations of HCV RNA measurements. Any HCV RNA threshold can be impacted by relatively large intra-patient, intra-laboratory and inter-assay variability in viral levels. In a multicenter study, 17% of patients changed HCV RNA category (based on 6,000,000 IU/ml) in the 30 days between collection of screening and baseline study samples, and the proportion of patients falling below that threshold varied depending on which licensed HCV RNA assay was used.(7) Ideally, by combining all relevant information, possibly including HCV RNA, the optimal treatment duration for a high probability of SVR could be selected for a given individual. While individualized therapy may appear to add complexity to patient care, development of computer-based algorithms that yield individualized estimates of success for a given regimen and duration of treatment might actually simplify clinical decision-making.

Other critical elements for implementing shorter therapies for chronic hepatitis C include determining optimal management for individuals who fail initial treatment and the willingness of insurers to pay for retreatment. Studies of shortened therapy should incorporate retreatment strategies for patients who fail to achieve SVR. Among 30 patients who relapsed after initial treatment with 8 weeks of ledipasvir/sofosbuvir, 80% responded to retreatment with 24 weeks of the same regimen.(7) Combining that retreatment rate to the ~95% efficacy seen after initial treatment of 8 weeks in ION-3 yields an overall response rate of ~99%, achieved after considerably fewer 'treatment-weeks' than required for an initial course of 12 weeks alone. In that retreatment study, failure was associated with the presence of NS5A RAVs, (7) suggesting that retreating such patients with a regimen that does not target NS5A might yield an even higher overall response rate. In another retreatment trial (SYNERGY), when patients who failed 4–6 weeks of ledipasvir/sofosbuvir plus one or two additional DAAs were retreated with ledipasvir/sofosbuvir alone for 12 weeks, 91% achieved SVR (intention-to-treat) even though most harbored NS5A RAVs.(8)

Insurer restrictions on retreatment could cause most patients to be over-treated to avoid permanent treatment failure for the small minority who fail initial treatment. A system that treats appropriately selected patients with a shortened course of therapy and allows retreatment of the few patients who fail initial treatment might allay fears of guidance panels about recommending shorter courses of therapy and also reduce healthcare costs.

In conclusion, an HCV RNA level <6,000,000 IU/ml, which is the basis for current prescribing information for 8 weeks of treatment with ledipasvir/sofosbuvir in the United States, is not statistically justified and should be reconsidered. To the extent possible, treatment recommendations should be based on well-powered, rigorous statistical analyses that consider all relevant variables. Effective strategies for treating selected patients with a shortened course of therapy might reduce treatment burden for the average patient and overall treatment costs.

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References

1. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. New England Journal of Medicine. 2014; 370:1879–1888. [PubMed: 24720702]
2. O'Brien TR, Lang Kuhs KA, Pfeiffer RM. Subgroup differences in response to 8 weeks of ledipasvir/sofosbuvir for chronic hepatitis C. Open Forum Infectious Diseases. 2014; 1
3. Hoofnagle JH, Sherker AH. Therapy for hepatitis C — the costs of success. New England Journal of Medicine. 2014; 370:1552–1553. [PubMed: 24725236]
4. US Food Drug Administration CDER. Statistical Review and Evaluation, NDA #: 205834 (Sofosbuvir and ledipasvir fixed-dose combination). 2014:28.
5. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatology. 2015; 63:199–236.
6. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015; 62:932–954. [PubMed: 26111063]
7. Lawitz E, Flamm S, Yang J, Pang P, Zhu Y, Svarovskaia E, et al. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks. J Hepatology. 2015; 62:S192.
8. Wilson EM, Kattakuzhy S, Sidharthan S, Sims Z, Tang L, McLaughlin M, et al. Successful retreatment of chronic HCV genotype-1 infection with ledipasvir and sofosbuvir after initial short course therapy with direct-acting antiviral regimens. Clinical Infectious Diseases. In press.

Table 1

Analysis of relapse rates among all patients receiving 8-week or 12-week regimens of sofosbuvir (SOF) and ledipasvir (LDV) with or without ribavirin (RBV) in ION-3, by baseline HCV RNA. Adapted from US Food Drug Administration CDER. Statistical Review and Evaluation, NDA #: 205834 (Sofosbuvir and ledipasvir fixed-dose combination)(4)

Baseline HCV RNA (IU/mL)	8-Week SOF/LDV & SOF/LDV+RBV (N=431)	12-Week SOF/LDV (N=216)	Proportion Difference (Exact 95% CI)[1]	P-value for Interaction[2]
< 1 million	0% (0/99)	0% (0/51)	0% (−7.8%, 3.8%)	not significant
≥ 1 million	5.9% (20/339)	1.8% (3/165)	4.1% (0.2%, 7.5%)	
< 1.5 million	0% (0/114)	0% (0/60)	0% (−3.3%, 6.7%)	not significant
≥ 1.5 million	6.4% (20/315)	1.9% (3/156)	4.4% (0.3%, 8.1%)	
< 2 million	1.4% (2/146)	1.4% (1/72)	0% (−6.6%, 3.7%)	0.34
≥ 2 million	6.4% (18/283)	1.4% (2/144)	5.0% (0.9%, 8.8%)	
< 2.5 million	1.9% (3/160)	1.2% (1/83)	0.7% (−4.9%, 4.4%)	0.46
≥ 2.5 million	6.3% (17/269)	1.5% (2/133)	4.8% (0.5%, 8.8%)	
< 3 million	1.7% (3/179)	1.1% (1/94)	0.6% (−4.3%, 4.0%)	0.46
≥ 3 million	6.8% (17/250)	1.6% (2/122)	5.2% (0.6%, 9.4%)	
< 3.5 million	1.5% (3/195)	1.0% (1/98)	0.5% (−4.2%, 3.6%)	0.44
≥ 3.5 million	7.3% (17/234)	1.7% (2/118)	5.6% (0.7%, 10.1%)	
< 4 million	1.9% (4/213)	0.9% (1/107)	0.9% (−3.6%, 4.2%)	0.53
≥ 4 million	7.4% (16/216)	1.8% (2/109)	5.6% (0.4%, 10.3%)	
< 5 million	2.1% (5/243)	0.8% (1/123)	1.2% (−2.7%, 4.1%)	1.0
≥ 5 million	8.1% (15/186)	2.2% (2/93)	5.9% (−0.1%, 11.4%)	
< 6 million	1.9% (5/260)	1.5% (2/131)	0.4% (−3.7%, 3.2%)	0.20
≥ 6 million	8.9% (15/169)	1.2% (1/85)	7.7% (1.9%, 13.3%)	
< 7 million	2.8% (8/286)	1.4% (2/145)	1.4% (−2.3%, 4.3%)	0.55
≥ 7 million	8.4% (12/143)	1.4% (1/71)	7.0% (0.2%, 13.2%)	
< 8 million	3.6% (11/306)	1.3% (2/151)	2.3% (−1.4%, 5.4%)	1.0
≥ 8 million	7.3% (9/123)	1.5% (1/65)	5.8% (−2.3%, 12.4%)	
< 9 million	3.8% (12/318)	1.3% (2/158)	2.5% (−1.3%, 5.6%)	1.0
≥ 9 million	7.2% (8/111)	1.7% (1/58)	5.5% (−2.9%, 12.4%)	
< 10 million	3.6% (12/332)	1.2% (2/166)	2.4% (−1.2%, 5.3%)	1.0
≥ 10 million	8.3% (8/97)	2.0% (1/50)	6.2% (−3.1%, 13.9%)	

[1] Based on inverting a two-sided test

[2] Based on Zelen's Test