Real-world effectiveness for 12 weeks of ledipasvir–sofosbuvir for genotype 1 hepatitis C: the Trio Health study

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Abstract
Early data regarding the “real-world” experience with novel therapies for hepatitis C (HCV) are encouraging. Data are still limited, however, regarding real-world rates of sustained virologic response (SVR) for ledipasvir–sofosbuvir (LDV-SOF), particularly for patients with prior treatment failure. We performed a retrospective cohort study of 1597 patients with chronic genotype 1 HCV who were treated using 12 weeks of the following regimens LDV-SOF±ribavirin (RBV) (n=1521 without RBV, n=76 with RBV). The primary outcome was SVR-determined at 12 weeks in an intention-to-treat design. Prescription according to Food and Drug Administration (FDA) approved labelling (adding RBV for patients with cirrhosis and treatment failure) was assessed in multivariate models. The study population was aged 60 years on average (range 19-89), 60% male, 50% Caucasian, 43% cared for at an academic centre and 30% cirrhotic. Overall, LDV-SOF resulted in a 94% SVR rate. Only 44 (2.9%) patients relapsed. LDV-SOF+RBV yielded SVR in 97% with 0 viral relapses. While cirrhosis and thrombocytopenia were associated with lower odds of SVR, in a multivariable regression model, only treatment at an academic centre and prescriptions contrary to FDA labelling—odds ratios, 0.56 95% CI (0.35-0.87) and 0.29 95% CI(0.12-0.68), respectively. The real-world experience with LDV-SOF mirrors the SVR rates observed in clinical trials. Efforts to promote prescription within FDA recommendations are warranted.

KEYWORDS
cirrhosis, ledipasvir, liver disease, ribavirin, sofosbuvir

1 | INTRODUCTION

Well-tolerated and highly efficacious direct-acting antiviral therapies have transformed the care of patients with hepatitis C (HCV).1–4 The patient experience of anti-HCV therapy has evolved from frequent treatment failures and adverse events to readily available cures without side effects.5,6 Importantly though, these data in support of direct-acting antivirals (DAAs) come predominantly from industry sponsored registration trials. Prior advances in the context of clinical trials such as the first-generation DAAs—boceprevir and telaprevir—were met with disappointing results when applied in “real-world” settings.7,10 The difficulty in translating trial experiences to the real-world led Kanwal and El Serag to describe an “unyielding” chasm between efficacy and effectiveness.11

There is reason to believe that the experience of the present generation of DAAs will prove different than the last. Early data regarding the “real-world” experience with novel DAAs are encouraging.12–14 Unfortunately, data are still limited regarding real-world SVR rates for LDV-SOF, the most frequently prescribed regimen. A recent study by

Abbreviations: BOC, boceprevir; LDV, ledipasvir; OMB/PTV/RTV and DSV, ombitasvir, paritaprevir, ritonavir and dasabuvir; PEG, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
Backus et al. demonstrated SVR rates of 93%-96% after 8-12 weeks of LDV-SOF in 4365 treatment-naïve patients from the Veterans Administration, effectively recapitulating the results of the ION-1 trial. Data are lacking, however, regarding treatment-experienced patients.

Herein, we present data from 1597 patients with chronic genotype 1 HCV who were treated with 12 weeks of LDV-SOF with or without RBV. Adverse events were defined as patients with prior treatment failure and cirrhosis. Only patients treated with 12 weeks of LDV-SOF without RBV were included. Prescriptions outside FDA-recommended labelling were defined as patients with prior treatment failure and cirrhosis. Any practice (solo or group) were characterized as community sites. Any other practice generally with pegylated interferon and RBV) and 30% were cirrhotic. The pretreatment demographics and clinical characteristics of the enrolled population are described in Table 1. In general, the population was aged 60 years on average (range 19-89), 60% male and 50% Caucasian. The majority of patients were treatment experienced (generally with pegylated interferon and RBV) and 30% were cirrhotic. Overall, 270 clinicians participated in the study across 31 states. Of the 1597 patients enrolled, 42% received their care in an academic facility. Forty-five (2.8%) were post-transplant at the time of therapy, and 104 (6.5%) were HIV co-infected. The clinical characteristics of patients seen at academic and community centres are delineated further in Supplementary Table 1. In general, patients at community centres were less likely to be cirrhotic, thrombocytopenic and treatment experienced.

Overall, the treatments were highly effective (Figure 1). LDV-SOF resulted in SVR12 in 94.1%. Treatment failure was observed in 44 patients with relapse (2.9%). Additionally, 33 (2.2%) were lost to follow-up, nine (0.6%) discontinued therapy and three (0.2%) died during therapy. LDV-SOF+RBV yielded SVR12 in 97.4% of 74 patients. Relapses were not observed in LDV-SOF+RBV; however, one (1.4%) patient was lost to follow-up and one (1.4%) discontinued therapy.

Subgroup analyses were performed to determine whether baseline clinical characteristics played a role in treatment success (Figure 2). Viewed as a cohort overall, the presence of cirrhosis (90.6% vs 95.9%, P<.0001), platelet count <100 000/mL (88.8% vs 95.0%, P<.0001), treatment in an academic centre (92.4% vs 96.0%, P<.0001) and treatment outside of FDA labelling recommendations (85.2% vs 95.1%, P<.0001) were each associated with lower SVR12. There were no statistically significant differences in SVR12 by age, gender, ethnicity and prior treatment experience, including those prior novel DAA-containing regimens (n=34, 85.3%) (all P values ≥.05). Compared to those without, neither HIV co-infection (98.0% vs 93.0%) nor liver transplant (98% vs 94%) had significant differences in terms of SVR12.

2 | METHODS

Endpoints were evaluated as “intention-to-treat” with the denominator including those who died, were lost to follow-up, discontinued treatment or relapsed after completion. Univariate comparisons were performed using chi-squared testing. Multivariable analyses were performed with backwards stepwise selection logistic regression procedure using covariates that were different with respect to SVR in their univariate comparison with P<.10. In view of the significance of adherence to FDA labelling recommendations in univariable analysis (and its relation to prior treatment experience), we included treatment experience in multivariable analyses. Multicollinearity was assessed by variable inflation factors (VIF). Among variables with elevated VIF (VIF >10%), the variable with the smaller effect was excluded from the model. Analysis was performed using JMP Pro®, Version 12. SAS Institute Inc., Cary, NC, 1989-2007.

3 | RESULTS
The clinical characteristics of these special populations are detailed in Supplemental Table 2. Finally, the state in which the patients were treated had no effect on their outcomes.

A multivariate analysis was performed to assess the adjusted impact of the significant variables on SVR. (Table 2) While the presence of cirrhosis, prior treatment experience, treatment at an academic centre and treatment outside of FDA recommendations were each numerically associated with lower odds of SVR, the relationships were only significant for the latter two. In a multivariable-adjusted analysis, patients treated at academic centres and those treated outside FDA labelling were 44% and 61% less likely to achieve SVR.

### DISCUSSION

Evidence increasingly supports the widespread uptake of highly effective, safe treatments for chronic HCV therapy.1–4,15–18 These “real-world” data suggest that there has been little difficulty in translating the results of clinical trials into a large cohort of diverse patients, many with prior treatment failure, from both academic- and community-based practice.

This study provides three novel findings. First, the observed SVR12 rates in clinical practice approximate those of the clinical trials even for patients with prior treatment failures. The SVR12 exceeded 94% in this cohort of racially diverse men and women from multiple different healthcare systems. Second, clinical outcomes were optimized by adherence to FDA labelling which was one of most powerful determinants of SVR12. Patients with cirrhosis and prior treatment failure should therefore receive LDV-SOF with RBV in accordance with FDA labelling recommendations. Accordingly, in order to optimize treatment effectiveness, interventions are warranted to ensure the use of RBV for appropriate candidates. Third, the subgroups with the lowest success rates (albeit strong relative to prior regimens) were those treated at an academic centre with cirrhosis. The negative association between SVR12 and treatment at an academic centre is hypothesis generating and may reflect unmeasured confounding comorbidities and severity of liver disease. Whereas both cirrhosis and thrombocytopenia were inversely related to SVR12 in univariable analyses, treatment at an academic centre took priority in the multivariable model suggesting that it may be a more complete marker of disease status and portal hypertensive complications than thrombocytopenia.

Four large studies have previously reported on the “real-world” outcomes with sofosbuvir-containing regimens for patients with chronic HCV. Two of these studies were nonrandomized registry studies with an observational design and the other two were randomized trials that included a real-world cohort. These studies were conducted in 165 different centers around the world and included 6127 individuals. The SVR12 rates were 89% and 90%, respectively. However, the real-world studies were limited in that they did not adjust for confounding variables. The current study is the first to include an academic centre cohort and allows for a more complete analysis of the impact of treatment at academic centres. This study is also the first to include a large cohort of racially diverse patients from multiple different healthcare systems.

### TABLE 1 Demographics and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>LDV-SOF n=1521</th>
<th>LDV-SOF+RBV n=76</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Academic practice—n (%)</strong></td>
<td>611 (40%)</td>
<td>65 (86%)</td>
</tr>
<tr>
<td><strong>Distinct states—n</strong></td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td><strong>Distinct physicians</strong></td>
<td>250</td>
<td>26</td>
</tr>
<tr>
<td><strong>Age—mean (range)</strong></td>
<td>60 (19-89)</td>
<td>59 (40-73)</td>
</tr>
<tr>
<td><strong>Male—n (%)</strong></td>
<td>868 (57%)</td>
<td>56 (74%)</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>234 (15%)</td>
<td>11 (14%)</td>
</tr>
<tr>
<td><strong>Hispanic/Latin</strong></td>
<td>100 (7%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>742 (49%)</td>
<td>52 (68%)</td>
</tr>
<tr>
<td><strong>Genotype—n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a (67%)</td>
<td>1017</td>
<td>57 (75%)</td>
</tr>
<tr>
<td>1b (28%)</td>
<td>433</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>1 Mixed (0%)</td>
<td>7</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1 (Unknown) (5%)</td>
<td>64</td>
<td>3 (4%)</td>
</tr>
<tr>
<td><strong>Initial viral load IU/mL—n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;800 K</td>
<td>389 (26%)</td>
<td>25 (33%)</td>
</tr>
<tr>
<td>800 K–6 million</td>
<td>795 (52%)</td>
<td>35 (46%)</td>
</tr>
<tr>
<td>&gt;6 million</td>
<td>326 (21%)</td>
<td>15 (20%)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>11 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Cirrhosis—n (%)</strong></td>
<td>448 (29%)</td>
<td>31 (41%)</td>
</tr>
<tr>
<td><strong>Platelets &lt;100 K/mL—no. (%)</strong></td>
<td>142 (11%)</td>
<td>15 (21%)</td>
</tr>
<tr>
<td><strong>Prior treatment failure—n(%)</strong></td>
<td>459 (30.2%)</td>
<td>46 (62.2%)</td>
</tr>
<tr>
<td><strong>PEG+RBV (n)</strong></td>
<td>305</td>
<td>26</td>
</tr>
<tr>
<td><strong>BOC+PEG+RBV (n)</strong></td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td><strong>TVR+PEG+RBV (n)</strong></td>
<td>51</td>
<td>10</td>
</tr>
<tr>
<td><strong>SMV+SOF (n)</strong></td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td><strong>SOF+PEG+RBV (n)</strong></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>SOF+RBV (n)</strong></td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td><strong>OMB/PTV/RTV and DSV (n)</strong></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>LDV-SOF (n)</strong></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Prior regimen unknown (n)</strong></td>
<td>48</td>
<td>1</td>
</tr>
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BOC, boceprevir; K, 1000, LDV, ledipasvir; OMB/PTV/RTV and DSV, om- bitasvir, paritaprevir, ritonavir and dasabuvir; PEG, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

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### FIGURE 1 Outcomes by Treatment Regimen

DC, discontinued, LDV, ledipasvir, LTFU, lost to follow-up, SVR, sustained virologic response

Patients treated with 12 weeks of therapy N = 1596

- LDV-SOF n = 1521
  - No SVR n = 44
  - SVR achieved n = 1432
  - Intention to treat: 94.1% Per protocol: 97.0%

- LDV-SOF+RBV n = 74
  - No SVR n = 0
  - SVR achieved n = 74
  - Intention to treat: 97.4% Per protocol: 100%

Death, n = 3
LTFU, n = 33
DC, n = 9
Death, n = 1
LTFU, n = 1
DC, n = 1
HCV, including three from the Veteran’s Administration (VA) and two examining LDV-SOF. Two studies, by Backus and Sulkowski studied the real-world results with SMV and SOF regimens. Neither study examined the effect of Q80K mutations or excluded patients with prior protease inhibitor experience. As a result, both studies reported SVR12 rates (71%-84%) that were lower than the clinical trial experience.

Real-world experience with LDV-SOF was explored in two prior studies, both from the VA. Butt and colleagues demonstrated 98.6% SVR12 in patients without cirrhosis and 93.8% in those with cirrhosis. As a result, both studies reported SVR12 rates (71%-84%) that were lower than the clinical trial experience.

The clearest representation of the real-world experience to date, however, was published by Backus et al. This group examined the VA cohort and included all 4635 treatment-naïve patients who received LDV-SOF, a group who was 96% male and 37% African American. The SVR12 rates were 91.3% for those taking LDV-SOF and 92.0% for those taking LDV-SOF+RBV. Like our cohort, Backus lacked detailed data regarding adverse events. Further, both this study and ours defined fibrosis stage using heterogeneous, generally noninvasive techniques. In contrast to the Backus study, our patients were enrolled by 270 clinicians across 31 states, representing numerous health systems across the US (both academic and community); three in 10 patients in our cohort experienced a prior treatment failure; and two in five patients were women.

Given the diversity of our cohort—wrt respect to sex, race, age and healthcare system—these data are likely generalizable to most clinical settings. However, the implications of these data must be interpreted in the context of the study design. First, we did not collect data from patients on haemodialysis and provide limited data with respect to post-transplant patients, two very important treatment subgroups.

**FIGURE 2** Predictors of Sustained Virologic Response—Univariate Associations. On the left, variables that were not significantly associated sustained virologic response (SVR) are presented. On the right, significant associations are presented: academic vs. community (P=.0001), platelet count < or ≥100 000/mL (P<.0001), cirrhosis or not (P<.0001) and treatment regimen (P=.001). The dotted line indicates the overall sustained virologic response rate (94%). HIV, human immunodeficiency virus.

**TABLE 2** Univariate and multivariate associations of clinical variables with sustained virologic response (SVR)

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0.41 (0.27-0.63)</td>
<td>.0001</td>
</tr>
<tr>
<td>Platelet count &lt;100 000</td>
<td>0.42 (0.25-0.72)</td>
<td>.002</td>
</tr>
<tr>
<td>Academic centre</td>
<td>0.51 (0.33-0.78)</td>
<td>.002</td>
</tr>
<tr>
<td>Outside FDA labelling</td>
<td>0.29 (0.18-0.51)</td>
<td>.0001</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>0.98 (0.63-1.51)</td>
<td>P=.93</td>
</tr>
</tbody>
</table>

The exposure variables chosen for a logistic regression of SVR were based on the significance of their univariate comparisons in Figure 2. The multivariate analysis depicts odds ratios that are adjusted for the other variables and prior treatment experience in a stepwise selection model. Platelet count and cirrhosis were collinear. Odds ratios less than 1 reflect inverse associations with SVR.
Second, although we collected data on prescriptions provided counter to FDA labelling, the reasons for which clinicians provided the medications outside FDA recommendations is unknown. Third, fibrosis was assessed in multiple different ways, often by noninvasive indices, each of which has its own false positives and negatives.\textsuperscript{21,22} Fourth, as in the study by Backus,\textsuperscript{15} we did not collect data on RBV dose reductions or safety events, although few patients discontinued therapy. Finally, we lack data on the specific reasons for treatment discontinuation which is fortunately rare.

In conclusion, the real-world experience of novel DAAIs in patients with chronic genotype 1 HCV mirrors that of the clinical trials. Interventions to ensure adherence with FDA labelling recommendations could further enhance the cost-effectiveness of therapy.

**DISCLOSURE**

Elliot Tapper is the guarantor of this article. No one other than the authors had any access to the model at any point.

**AUTHOR CONTRIBUTIONS**

Afdhal proposed the concept. Tapper, Lee and Guest performed the analysis. Afdhal, Bacon, Curry, Dieterich, Flamm, Kowdley, Tsai and Younossi performed data acquisition. Tapper wrote the article. Afdhal, Bacon, Curry, Dieterich, Flamm, Kowdley, Tsai and Younossi performed critical revision.

**CONFLICTS OF INTEREST**

Dr. Tapper reports receiving has no conflicts; Dr. Bacon reports receiving research support from Merck, Gilead Sciences Inc., Bristol-Myers Squibb, and AbbVie and consulting, speakers bureau and advisory board/data safety monitoring board membership from Merck, Gilead Sciences Inc., Bristol-Myers Squibb, ISIS Pharmaceuticals, AbbVie, Valeant Pharmaceuticals, Trio Health and Janssen Pharmaceuticals; Dr. Curry reports receiving consulting fees from Gilead Sciences, AbbVie, Bristol-Myers Squibb and research grants from Gilead Sciences, MassBiologics and Conatus; Dr. Dieterich reports receiving grant support or consulting fees from Gilead Sciences, Bristol-Myers Squibb, AbbVie, Merck, Trio Health and Janssen Pharmaceuticals; Dr. Flamm reports receiving grant support form Gilead Sciences Inc, AbbVie, Bristol-Myers Squibb and Merck and consulting fees from Gilead Sciences Inc, AbbVie, Bristol-Myers Squibb, Merck, Trio Health and Janssen; Ms. Guest reports receiving grant support from Gilead Sciences and AbbVie and she is an employee of Trio Health; Dr Tsai reports receiving advisory and speakers bureau fees from Gilead Sciences, Bristol-Myers Squibb, AbbVie, Merck, Intercept Pharmaceuticals, Janssen Pharmaceuticals, Bayer, Trio Health and Valeant/Salix Pharmaceuticals and grant support from Gilead Sciences, Bristol-Myers Squibb, AbbVie, Merck, Intercept Pharmaceuticals, Janssen Pharmaceuticals and Bayer and receives grant support from Gilead Sciences Inc, Bristol-Myers Squibb, AbbVie, Merck, Intercept Pharmaceuticals, Janssen Pharmaceuticals and Bayer; Dr. Younossi, receiving consulting fees from Gilead Sciences, AbbVie, Intercept Pharmaceuticals, Bristol-Myers Squibb, Trio Health and GlaxoSmithKline PLC; Dr. Afdhal reports receiving grant support from Gilead Sciences Inc, AbbVie, and Bristol-Myers Squibb and consulting/advisory board fees from Merck, Gilead Sciences Inc, Echosens, GlaxoSmithKline PLC, Ligand Pharmaceuticals, Inc, Janssen Pharmaceuticals Inc, Roivant Sciences Inc, Co-Crystal Pharma Inc, Trio Health and Shionogi, Inc and being employees of and having an equity interest in Springbank Pharmaceuticals, equity interested in Allurion Technologies.

**REFERENCES**


SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.