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Effectiveness of Ledipasvir-Sofosbuvir Combination in Patients With Hepatitis C Virus Infection and Factors Associated With Sustained Virologic Response

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Abstract

BACKGROUND & AIMS—The combination of ledipasvir and sofosbuvir has been approved for treatment of genotype 1 hepatitis C virus (HCV) infection, including an 8-week regimen for treatment-naïve patients without cirrhosis and a baseline level of HCV RNA <6 million IU/mL. We analyzed data from a multicenter, prospective, observational study to determine real-world sustained virologic responses 12 weeks after treatment (SVR12) with regimens containing ledipasvir and sofosbuvir and identify factors associated with treatment failure.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.08.004.

Conflicts of interest

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METHODS—We collected data from 2099 participants in the HCV-TARGET study with complete virologic data (per-protocol population). We analyzed data from 1788 patients receiving ledipasvir-sofosbuvir (282 for 8 weeks, 910 for 12 weeks, 510 for 24 weeks, and 86 for a different duration) and 311 receiving ledipasvir-sofosbuvir plus ribavirin (212 for 12 weeks and 81 for 24 weeks, 18 for other duration) to estimate SVR12 (with 95% confidence interval [CI]), and logistic regression methods to identify factors that predicted an SVR12.

RESULTS—The overall study population was 25% black, 66% with HCV genotype 1A infection, 41% with cirrhosis, 50% treatment-experienced, and 30% receiving proton pump inhibitors at start of treatment. In the per-protocol population, SVR12s were achieved by 96% of patients receiving ledipasvir-sofosbuvir for 8 weeks (95% CI, 93%–98%), 97% receiving the drugs for 12 weeks (95% CI, 96%–98%), and 95% receiving the drugs for 24 weeks (95% CI, 93%–97%). Among patients also receiving ribavirin, SVR12 was achieved by 97% of the patients receiving the drugs for 12 weeks (95% CI, 94%–99%) and 95% receiving the drugs for 24 weeks (95% CI, 88%–99%). Of the 586 patients who qualified for 8 weeks of treatment, only 255 (44%) received the drugs for 8 weeks. The rate of SVR12 among those who qualified for and received 8 weeks of therapy was similar in those who qualified for 8 weeks but received 12 weeks therapy (96%; 95% CI, 92%–99% vs 98%; 95% CI, 95%–99%). Factors that predicted SVR12 were higher albumin (≤3.5 g/dL), lower total bilirubin (≥1.2 g/dL), absence of cirrhosis, and absence of proton pump inhibitor use.

CONCLUSIONS—Regimens containing ledipasvir and sofosbuvir are highly effective for a broad spectrum of patients with HCV genotype 1 infection treated in different clinical practice settings. Expanded use of 8-week treatment regimens for eligible patients is supported by these real-world results. Modification of proton pump inhibitor use may increase rates of SVR. ClinicalTrials.gov no. NCT01474811.

Keywords

DAA; NS5A Inhibitor; NS5B Inhibitor; Antiviral

Ledipasvir-sofosbuvir (LDV/SOF) was approved for treatment of genotype 1 chronic hepatitis C virus (HCV) infection in October 2014. Its approval provided the first “one pill a day” regimen for 12 weeks as treatment for chronic HCV. LDV/SOF also provided an opportunity to consider 8 vs 12 weeks treatment for patients with favorable clinical and virologic characteristics. Specifically, in the ION-3 study, treatment-naïve patients with nonadvanced fibrosis (F0-3) and baseline HCV RNA <6 million IU/mL treated for 8 weeks were shown in a post-hoc analysis to have SVR12 rates of 97% compared with 96% in similar patients treatment for 12 weeks.[1]

Important gaps in our knowledge about use of LDV/SOF in clinical practice remain. Key among these gaps is the “real-life” efficacy of the 8-week regimen, as well as how frequently it is being utilized by clinicians, and what factors may be influencing decisions regarding use of short vs longer duration therapy and inclusion/exclusion of ribavirin. Indeed, the lack of confirmatory data on the efficacy of the 8-week regimen may have contributed to the Infectious Diseases Society of American/American Association for the Study of Liver Diseases HCV guidance not recommending this regimen.[2] Additionally, as the real world of

patients have a greater array of medical comorbidities, prior treatment exposures, and more variable adherence with all oral regimens, the safety and discontinuation rates in clinical practice may be predicted to be quite different from the registration trials. Finally, there remains a need to determine the baseline and on-treatment factors that may affect the rates of virologic failure, in particular those factors that are potentially modifiable.

Ledipasvir, an NS5A inhibitor, requires an acid environment for absorption. In the original clinical trials, all patients had to be off proton pump inhibitors (PPIs) for at least 4 weeks before the start of LDV/SOF therapy. The package insert for LDV/SOF highlights the importance of the acid environment and provides specific guidance on dosing of PPIs (and other acid-reducing agents) during LDV/SOF therapy. These guidelines were not explicitly studied in the registration trials, so real-world data may be helpful in understanding this important drug–drug interaction.

In this HCV-TARGET consortium study, we examined the real-world clinical experience with LDV/SOF-containing regimens to assess their efficacy (SVR12) and safety in HCV genotype 1–infected patients and to determine baseline factors associated with virologic failure.

Methods

Study Population and Design

HCV-TARGET is a longitudinal, observational study of chronic hepatitis C patients that began in December 2011 and is ongoing. This consortium of academic (n = 44) and community (*n* = 17) centers from North America (n = 57) and Europe (n = 4) is collecting data for regimens used in this rapidly changing therapeutic area. Prospective data were captured from enrolled patients using a common database that utilized novel, standardized source data abstraction as described previously.[3,4] All captured data was managed using Research Electronic Data Capture, with electronic data capture tools hosted at UNC Chapel Hill. Research Electronic Data Capture is a secure, web-based application designed to support data capture for research studies.[5] A centralized team of trained coders reviews all redacted medical records obtained from participating sites for data entry and systematically monitors the data entries for completeness and accuracy. All records were screened for extreme or unlikely values and verified/resolved with additional queries. The study protocol did not define specific populations, regimens, dosing, and duration or safety management.

For this analysis, patients were eligible if they were 18 years or older, infected with HCV genotype 1, and treated with LDV/SOF or LDV/SOF plus ribavirin (RBV). The cohort sample size was not determined a priori, but rather reflects the need for timely information about LDV/SOF safety and efficacy in real-life clinical settings to the larger “treating” community.

To be included in this analysis, patients had to have completed LDV/SOF-based treatment before January 2016. Patients who discontinued treatment prematurely for any reason were excluded to avoid unbiased assignment to a specific treatment duration group and sufficient time for post-treatment follow-up. Demographic characteristics, laboratory values (baseline

and on treatment), and adverse events were collected and analyzed by treatment regimen for the evaluable population (n = 2255), which was composed of all patients who completed treatment. Treatment efficacy in evaluable population was evaluated among patients with available outcomes (n = 2180). Patients lost to post-treatment follow-up were counted as nonvirologic treatment failures. The per-protocol population (n = 2099) was composed of the patients in the evaluable population who had a virologic outcome. Associations between SVR and baseline risk factors are reported for the per-protocol population. The unadjusted overall rates of SVR, as well as for subgroups based on treatment history and presence of cirrhosis, were calculated for the evaluable and per-protocol populations. Furthermore, the unadjusted SVR rates were calculated for the per-protocol population for subgroups of interest, particularly based on but not limited to baseline viral load, HCV virus subtype, and use of PPI at baseline.

Treatment Regimens

The choice of LDV/SOF was at the discretion of the local treating physician, as was use of RBV. Similarly, treatment duration was determined by the treating physician and, for the purposes of analysis, was defined as 8 weeks (±7days), 12 weeks (±7days), 24 (±7days), or other (not meeting these windows). Patients received the fixed-dose combination of LDV/SOF (90/400 mg) once daily. For those receiving RBV, dosing varied across patients and treatment centers; however, for most patients, RBV was administered according to body weight (<75 kg, 1000 mg daily in 2 divided doses; ≥75 kg, 1200 mg daily in 2 divided doses).

Measurements

Demographic, clinical, adverse event, and virologic data were collected at baseline and as available every 12 weeks throughout the treatment period and the post-treatment follow-up. Laboratory data, collected per standard practice, included levels of serum creatinine, albumin, total bilirubin, alanine and aspartate aminotransferase levels, hemoglobin, platelet count, and HCV RNA. Concomitant medications were collected from each visit. Specifically, in reference to PPI use, the presence of PPI in the concomitant medications list at initiation and during HCV therapy was recorded; duration, dose, and frequency also were recorded when available. Information on timing of antacid administration in relationship to LDV/SOF was not available.

The presence of cirrhosis was defined at the time of enrollment by biopsy and/or a combination of clinical, laboratory, elastography, and imaging criteria established a priori.[3] Patients were determined to have cirrhosis if they had evidence of stage 4 fibrosis by liver biopsy at any time before therapy; evidence of stage 3 fibrosis by liver biopsy at any time before therapy with any of the following criteria: platelet count <140,000 per μL, presence of esophageal varices on esophagogastroduodenoscopy, evidence of cirrhosis and/or portal hypertension and/or of ascites by imaging studies, FibroSure (or equivalent) test, vibration-controlled transient elastography, or equivalent compatible with stage 4 fibrosis; or in the absence of liver biopsy, any 2 of the following criteria: platelets count <140,000 per μL, presence of esophageal varices on esophagogastroduodenoscopy, evidence of cirrhosis and/or portal hypertension and/or ascites by imaging studies, Fibro-Sure or equivalent test,

vibration-controlled transient elastography, or equivalent compatible with stage 4 fibrosis. History of hepatic decompensation was defined as evidence of prior or current diagnosis of ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or variceal hemorrhage, or baseline concomitant medications with a specific use listed for these indications.

Adverse events (AE), defined as any new symptom or event recorded in the medical record that occurred during the HCV treatment period, were collected and reported regardless of the need or lack thereof for a prescription medication or a dose reduction or discontinuation of HCV treatment. AEs recorded in the patient clinical note were identified by HCV-TARGET data abstractors and then entered into the database as text and further coded by the clinically validated international medical terminology dictionary, MedDRA (the Medical Dictionary for Regulatory Activities). Serious AEs were defined as any AE that required hospitalization or met criteria for expedited reporting per FDA form MEDWATCH 3500.

Primary Study Outcomes

The efficacy end point was SVR defined as a plasma HCV RNA level below quantitation or undetectable at least 64 days after treatment completion (SVR12). For patients who did not achieve SVR12, the frequency of relapse, virologic breakthrough, and virologic nonresponse were reported, as were patients lost to follow-up evaluation. The safety end points included common LDV/SOF AEs, including fatigue, headache, and nausea; anemia AEs; cardiac events, need for ribavirin dose reductions or discontinuation; and any serious AEs, hepatobiliary serious AEs, and death.

Analytic Approach

Demographic characteristics, laboratory values, and AEs were collected and analyzed by treatment regimen for the evaluable population.

The unadjusted rates of SVR were calculated for the LDV/SOF and LDV/SOF-RBV per-protocol population and evaluable population, as well as for subgroups of interest, particularly based on treatment history (treatment-experienced, treatment-naïve), the presence of cirrhosis (yes, no). For subgroups of interest based on baseline HCV RNA (<6, ≥6 million IU/mL), history of liver transplantation (yes, no), history of hepatic decompensation event status (decompensated, non-decompensated), history of taking PPIs at baseline (no, yes), and duration of treatment (8 weeks, 12 weeks, 24 weeks) unadjusted SVR rates are presented for the LDV/SOF and LDV/SOF-RBV per-protocol population only. Confidence intervals (CIs) of unadjusted rates were calculated using exact binomial methods.

Multivariable analyses (age- and sex-adjusted) of SVR were performed for the LDV/SOF per-protocol population and associations between every baseline covariate and SVR outcome were estimated with logistic regression using Firth penalized maximum likelihood estimation of the effect of a covariate of interest with adjustment for age and sex.[6] The set of covariates was selected a priori based on a consensus of clinical expertise and included the most well-established baseline covariates associated with SVR: sex, age, HCV genotype subtype (a or b), albumin (<3.5 g/dL, ≥3.5 g/dL), platelet count (1000/uL), total bilirubin (≤1.2 mg/dL, ≥1.2mg/dl), hemoglobin (g/dL), baseline HCV RNA (<6, ≥6 million IU/mL),

cirrhosis status, a history of antiviral treatment, history of hepatic decompensation, body mass index (kg/m^2), and baseline PPI use (yes, no). Subsequently, additional variables of PPI use were evaluated including any PPI use (yes, no), daily omeprazole dose equivalent (≤20 mg, >20 mg), PPI dose frequency (once, twice daily) and fraction of treatment time on PPI.

Auxiliary sensitivity analyses were performed to evaluate the sensitivity of the primary results (ie, effects of multiple predictors on SVR) to reasonable perturbations of the statistical methods and assumptions used. Specifically, 2 alternative models were considered and their results were compared with the primary results. First, we tested whether a possible selection bias in our observational study influenced our main results. Selection bias was addressed through applying inverse probability weighting approach, allowing for the creation of pseudorandomization.[7] In this approach, a weight is calculated for each individual such that all prespecified predictors of PPI use become balanced in groups with and without PPI use. All risk factors used in the model are presented in the Supplementary Figure 4. Finally, the effect of PPI use is estimated for pseudorandomized groups, that is, with logistic regression using the individual weights. Second, the Lasso penalized generalized linear model was used to identify a set of smaller number of baseline covariates (among the ones used in the inverse probability weighting model), thus providing optimal multivariable generalized linear model for not achieving SVR.[7] The Lasso penalized estimation produced a parsimonious model with 6 baseline covariables: total bilirubin, albumin, history of previous treatment, sex, PPI use, and HCV genotype subtype, excluding all other prespecified covariates listed here. Multiple imputation was used to address missing values in baseline variables of interest in these sensitivity analyses. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

Informed Consent

The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The independent ethics committee at each participating study center or a central Institutional Review Board approved the protocol if a local Institutional Review Board was not in place. All patients provided written informed consent for their participation. All authors had complete access to the study data, and reviewed and approved the final manuscript.

Results

Before January 2016, a total of 2356 patients ended treatment with a LDV/SOF-containing regimen; 2289 patients completed treatment, and 67 (2.8%) discontinued therapy early. Thirty-four patients who completed treatment had insufficient follow-up time to assess for SVR12 (Supplementary Figure 1), resulting in 2255 patients in the evaluable population. Due to variability of standard follow-up practice at the sites, 75 of the 2255 patients were still in post-treatment follow-up at the time of reporting, and 81 were lost to follow-up, resulting in a final efficacy cohort of 2099 patients (per-protocol population).

The vast majority (86%) of the evaluable population received treatment with LDV/SOF alone (1927 of 2255), with only 328 of 2255 (14%) receiving LDV/SOF-RBV

(Supplementary Figure 1). Actual treatment duration among the LDV/SOF-treated patients was 8 weeks in 305 of 1927 (16%), 12 weeks in 971 of 1927 (50%), 24 weeks in 552 of 1927 (29%), and other in 99 of 1927 (5%). Among 328 patients treated with LDV/SOF-RBV, the actual duration of therapy was 8 weeks in 2 of 328 (<1%), 12 weeks in 222 of 328 (68%), 24 weeks in 85 of 328 (26%), and other in 19 of 328 (6%) (Supplementary Tables 1 and 2).

Of the evaluable population, 60% were male, median age was 60 years, 24% were aged 65 years or older, and 25% were black race. The majority of the cohort was infected with genotype 1A (66%), with a median HCV viral load of 6.2 $\log_{10}$ IU/mL and 85% with HCV viral load <6 million IU/mL. A total of 41% of patients had cirrhosis, 50% treatment-experienced including 14% direct-acting antiviral treatment-experienced, 18% with a history of hepatic decompensation, and 13% had received a prior liver transplantation (Table 1). Compared with patients receiving LDV/SOF, patients receiving RBV with LDV/SOF were more frequently treatment-experienced (67% vs 47%) and cirrhotic (58% vs 38%), had lower baseline platelet counts (median 133 vs 176 × $10^3/\mu L$), history of hepatic decompensation (29% vs 17%), or a prior liver transplantation (48% vs 7%) (Table 1). Human immunodeficiency virus co-infection was infrequent in the cohort (4%). PPI at baseline was reported in 30% of patients, observed slightly more frequently in patients treated with LDV/SOF-RBV (37% vs 29%). Among LDV/SOF PPI users (n = 550), 506 of 550 (92%) were taking the PPI at baseline and the PPI duration and baseline dose were available in 81% (444 of 550) and 80% (440 of 550), respectively. Among these PPI users, 41% (182 of 440) were on an omeprazole dose equivalent to >20 mg/d and 89% (396 of 444) were on their PPI during the whole treatment time (Table 1).

Patient characteristics by treatment duration varied. Among LDV/SOF-treated patients (Supplementary Table 1), the 24-week vs 12-week treatment group was more frequently treatment-experienced (90% vs 36%), cirrhotic (76% vs 27%), and with history of hepatic decompensation event (34% vs 11%). The 8-week treatment arm was 96% treatment-naïve, 99% without cirrhosis, and 96% with viral load <6 million IU/mL). Among LDV/SOF-RBV–treated patients (Supplementary Table 2), the 24- vs 12-week treatment group was more frequently treatment-experienced (91% vs 59%), cirrhotic (74% vs 52%), and with a history of hepatic decompensation event (48% vs 22%).

Efficacy Outcomes

Of the 2255 patients forming the evaluable population, 2180 had treatment outcomes available, and the overall SVR12 rate was 93% (Supplementary Table 3). In the per-protocol, the SVR12 rate was 96% (95% CI, 95%–97%) among 1788 treated with LDV/SOF and 97% (95% CI, 94%–99%) among 311 treated with LDV/SOF plus RBV. In the LDV/SOF group, the SVR12 rates were 96% (95% CI, 93%–98%) in those treated for 8 weeks (271 of 282), 97% (95% CI, 96%–98%) in patients treated for 12 weeks (881 of 910) and 95% (95% CI, 93%–97%) in those treated for 24 weeks (486 of 510). In the LDV/SOF-RBV group, the SVR12 rates were 97% (95% CI, 94%–99%) in those treated for 12 weeks (206 of 212) and 95% (95% CI, 88%–99%) in those treated for 24 weeks (77 of 81) (Figure 1). The majority of the treatment failures were due to relapse. A total of 6 patients never achieved an HCV

RNA below limits of quantitation and 1 patient experienced a viral breakthrough (Supplementary Table 3). Of patients receiving LDV/SOF plus RBV, 39% had an RBV dose reduction and 9% RBV discontinued. The SVR rates in those with no change, reduction, and discontinuation of RBV were 95.7%, 98.4%, and 96.3% (data not shown).

A total of 586 patients were treatment-naïve, non-cirrhotic, and had a baseline HCV RNA <6 million IU/mL and thus qualified for treatment with LDV/SOF for 8 weeks. Among the patients possibly eligible to receive 8 weeks of therapy, only 255 (44%) received 8 weeks therapy, while 296 (51%) were treated for 12 weeks, 10 patients (2%) were treated for 24 weeks, and 25 (4%) patients received treatment with nonstandard treatment duration. Physicians' rationale for prescribing 12 vs 8 weeks of therapy was not collected. Among the subgroup that qualified for 8 weeks of treatment, the SVR12 rate was 96% (95% CI, 94%–99%) in the group who received 8 weeks (244 of 255) and 98% (95% CI, 95%–99%) in the group who received 12 weeks (289 of 296). We examined the relationship between week-4 HCV-RNA results (early virologic response) and duration of therapy. Among 255 patients who qualified for 8 weeks of treatment and received 8 weeks, 158 had week-4 HCV-RNA available; 5% of these patients (n = 12) had a quantifiable HCV-RNA result. Among the 296 patients who qualified for 8 weeks treatment and received 12 weeks, 189 had week 4 HCV-RNA available: 9% of these patients (n = 25) had quantifiable HCV-RNA at week 4. This suggests that the HCV-RNA results at week 4 were unlikely to be driving decision-making about use of 12 weeks of therapy in patients who qualified for 8 weeks. Of note, a quantifiable HCV-RNA result at week 4 was not predictive of relapse in either the 8-week or 12-week group, as only 1 patient (treated for 12 weeks) who still had quantifiable week-4 HCV-RNA relapsed. Two patients (1 treated for 8 weeks and 1 treated with 12-week regimen) were nonresponders. Twenty-three patients were treated for 8 weeks who did not meet acceptable criteria for shorter duration therapy; all 23 patients achieved SVR.

Among those treated with LDV/SOF, the SVR12 rates varied by presence of cirrhosis, subgenotype, prior transplantation, history of hepatic decompensation, and baseline PPI use (Figure 2). Crude SVR rates, in per-protocol population, were lowest (<95%) among those with cirrhosis (94%; 95% CI, 91%–95%), prior liver transplantation (94%; 95% CI, 89%–98%), history of hepatic decompensation (90%; 95% CI, 86%–93%), and PPI use (94%; 95% CI, 91%–96%). In age- and sex-adjusted multiple logistic models, the factors significantly associated with SVR were albumin –3.5 g/dL (odds ratio [OR], 4.7, 95% CI, 2.79–7.90), total bilirubin –1.2 g/dL (OR, 3.7; 95% CI, 2.20–6.15), absence of cirrhosis (OR, 2.97; 95% CI, 1.81–4.99), no-decompensated liver disease (OR, 4.15; 95% CI, 2.52–6.77), and PPI use (OR, 0.41; 95% CI, 0.25–0.67) (Figure 3).

Because baseline PPI use was likely not random, we addressed this potential bias by applying inverse probability weighting to create a "pseudo randomized population" in which other baseline predictors of SVR were balanced among the 2 groups. In this analysis, restricted to patients treated with LDV/SOF, use of PPI was associated with an approximately 2-fold lower odds of achieving SVR compared with those with no use of PPI (OR, 0.57; 95% CI, 0.25 to 0.67) (Supplementary Figure 3). In a second subanalysis to address the association between of PPI and SVR, multiple Lasso regression was used to identify the most significant predictors of SVR12. The final multiple logistic model

identified a combination of 3 baseline factors significantly associated with SVR12: nonuse of PPI (OR, 0.62; 95% CI, 0.37 to 1.03), higher albumin level (OR, 2.43; 95% CI, 1.61 to 3.66), and lower bilirubin level (OR, 0.72; 95% CI, 0.58 to −0.89) (Supplementary Figure 4). The crude SVR rates in the per protocol population of those treated with LDV/SOF plus RBV varied from 92.5% to 100% among different subgroups (Supplementary Figure 2).

Safety Outcomes

Of the 2356 patients who ended treatment, 2.8% (n = 67) discontinued treatment early, with similar frequency of treatment discontinuation in those taking RBV and those not (1% [n = 4 of 337] and 3% [n = 63 of 2019], respectively). There were 13 deaths; 12 were in patients with cirrhosis, 7 had decompensated cirrhosis at baseline. The 1 death in the LDV/SOF-RBV was related to a traffic accident. The causes of deaths in the LDV/SOF group were attributed to acute respiratory failure, metastatic breast cancer, coronary artery disease, cerebral hemorrhage, subdural hemorrhage, multi-organ failure, sepsis, septic shock, narcotic overdose, and a traffic accident. Two patients died of unknown causes. Adverse events were reported in 63% of patients in the evaluable population on LDV/SOF and 85% of LDV/SOF-RBV, with higher frequencies of fatigue and anemia in the group receiving RBV (Table 2). There were 3 patients with reported bradyarrhythmias: 2 with bradycardia and 1 with sick sinus syndrome. There were no reported cases of lactic acidosis, but there was 1 case of increased blood lactic dehydrogenase.

In the evaluable population, serious AEs were reported in 5% in those receiving LDV/SOF and in 9% in those receiving LDV/SOF-RBV. Most serious AEs occurred among patients with cirrhosis at baseline.

Discussion

The FDA approval of LDV/SOF in October 2014 signaled yet another advance in the treatment of HCV infection, with a safe and simple regimen that achieved high rates of SVR in persons infected with genotype 1. The phase 3 studies leading to the approval of this fixed-dose combination therapy reported SVR12 rates with 12 weeks treatment of 95% (95% CI, 92%–98%) in treatment-naïve[1] and 94% (95% CI, 91%–99%) in treatment-experienced[7] genotype 1 patients.[8] As clinical trials generally select for patients with fewer comorbidities and high adherence rates and are conducted by experienced investigators, the question of whether these high rates of SVR would be achieved in “real world” settings comes to the fore. Our results, reflecting an unselected patient population treated in a variety of treatment settings, both academic and community, indicates that SVR rates with this simple regimen appear to be as high as those seen in the clinical trials, with SVR12 rates of 96% (95% CI, 95%–97%) in patients treated with LDV/SOF with or without RBV. Moreover, treatment discontinuation was extremely low at 2.8%, attesting to the much improved tolerability and convenience of this regimen.

An important finding emerging from this HCV-TARGET cohort study was the high efficacy of the 8 weeks LDV/ SOF regimen, with an overall SVR rate of 96% (95% CI, 93%–98%). This is comparable with that achieved in the prior clinical trial, in which overall SVR in noncirrhotic patients was 94% (95% CI, 90%–97%) with 8 weeks of LDV/SOF.[1] Based on a

post-hoc analysis, the rates of relapse were shown to be lowest for those treated with 8 weeks that had pretreatment HCV RNA level <6 million IU/mL. This led to the approved indication for LDV/SOF for 8 weeks being noncirrhotic, genotype 1 patients who were treatment-naïve and with a baseline HCV RNA level of <6 million/mL. In that subgroup, the SVR12 rate with 8 weeks treatment was 97%, a result similar to that achieved in our study. This supports the use of 8 weeks of therapy in this group of patients and represents a substantial cost savings compared with 12 weeks of therapy.

What is clear from our study is that the 8-week regimen is underutilized, with only 44% of those who meet eligibility for 8-week duration therapy actually receiving it, and a substantial proportion of patents being overtreated and receiving a longer treatment course. The reasons for the underutilization of 8 weeks of therapy in eligible patients are not clear, but may reflect provider confidence in the registration data. Alternatively, because many clinicians come from an era of using on-treatment virologic responses to guide treatment, we hypothesized that clinicians might be using HCV RNA results at week 4 to guide their decisions on treatment. However, our data do not support this hypothesis. It is hoped that with the additional data from our study and those of other real-life cohorts, clinicians will see the benefit of short-course therapy for their noncirrhotic treatment-naïve patients. The use of the “6 million IU/mL” cutoff for determining eligibility for shorter duration therapy have been called into question,[9] as the post-hoc analysis used to generate this cutoff was likely underpowered to adjust for all the factors contributing to SVR12. Despite this, our results suggest that this cutoff can be used in decision-making and will yield high SVR rates in appropriately selected patients. Given the high SVR rate seen, the question to be answered by future analyses of combined larger data sets, is whether a higher cutoff, allowing more patients to be treated for 8 weeks, may be used and still achieve high SVR rates. In our study, only 13 (5%) patients receiving the 8-week regimen had an HCV viral load >6 million IU/mL, thus not allowing us to examine whether higher viral load cutoffs might be considered.

Another unexpected but important finding of our study was the significant impact of PPI use on SVR rates. Ledipasvir’s solubility decreases as pH increases and, consequently, acid-reducing agents can affect drug absorption and drug levels. Thus, for patients on a PPI, it is recommended that the dose not be higher than omeprazole 20 mg daily (or equivalent) and taken fasting at the same time as LDV/ SOF.[10] Whether patients are aware of this requirement and are able to follow these requirements is unknown. PPI use was frequent in HCV-TARGET with approximately 1 in 4 patients on a PPI at initiation of HCV therapy and those on PPIs had approximately 2-fold lower odds of SVR than those who were not. Additionally, a dose equivalent higher than omeprazole 20 mg daily and twice daily dosing of PPI therapy were associated with lower odds of SVR. This translates into an absolute difference in SVR between those on and off PPIs of 4% and although this may be viewed as a modest difference in SVR, it is an important observation because it represents one of a few modifiable factors associated with SVR. At a minimum, providers should ensure patients are educated on the importance of the appropriate doses of PPI and take the PPI as recommended to minimize any impact on LDV absorption. Additionally, providers should consider whether PPI therapy is essential for a given patient and withdraw PPI use in the absence of an indication. Of note, the reason for PPI use was not captured in this study and

patients with strong indications for use, such as patients with recent gastrointestinal bleeding, may be included.

Patients with cirrhosis, especially those with decompensated cirrhosis, have lower rates of SVR with currently available all oral combination therapies. In the clinical trials of LDV/SOF with and without RBV in compensated cirrhotics, SVR12 was achieved in 95% of treatment-naïve patients receiving 12 weeks of therapy and 98% in patients receiving 24 weeks, but with previously treated patients with cirrhosis, the addition of RBV was needed to achieve SVR >90%.[11,12] In our analysis, the per-protocol SVR rate in the SOF/LDV with/without RBV (all treatment lengths) was 94%–97% in cirrhotics vs 97%–98% in noncirrhotics, and those with decompensated cirrhosis was 90%–97%. Within the patients with cirrhosis, the SVR rate in the LDV/SOF with and without RBV in patients treated for 12 weeks was 97% and 93%, respectively, and those treated for 24 weeks had SVR rates of 95% and 94%, respectively (not shown). These results again suggest that “real-life” results with LDV/ SOF in cirrhotic patients are comparable with those achieved in prior clinical trials.

As highlighted by the very low rate of early treatment discontinuation, side effects are rarely treatment-limiting. Adverse events are reported in the majority of patients, and with higher frequency in patients receiving RBV as part of the regimen. The well-known side effect of anemia and associated symptoms, such as fatigue and dyspnea, were among the most frequently cited side effects. Quality of life measures were not captured in this observational cohort study, but prior studies have highlighted the negative impact of RBV on physical and psychosocial functioning. Thus, there remains a strong desire on the part of clinicians to eliminate the need for RBV. Although this has been achieved for most HCV-infected populations, those with cirrhosis, especially those treatment-experienced or with a history of hepatic decompensation, as well as transplant recipients, are typically groups needing RBV to achieve the highest SVR rates. Of course, these same groups are the patients often less able to tolerate RBV due to concurrent hypersplenism, gastrointestinal bleeding, and renal dysfunction. Thus, identifying new combinations, aimed at targeting 3 or more enzymatic targets, may provide sufficient efficacy to displace RBV from future regimens.

In this large observational study, we have shown that LDV/SOF is highly effective in a wide spectrum of patients and treatment settings. SVR rates parallel those achieved in clinical trials, demonstrating how effectively this regimen has translated in clinical practice. However, continued efforts to optimize the use of HCV therapies are needed. The 8-week regimen achieved excellent SVR rates but was underutilized, and clinicians are encouraged to use the shorter treatment course in appropriate patients—those who are treatment-naïve, noncirrhotic, and with HCV viral load <6 million IU/mL. Clinicians should be attentive to the use of PPIs, as this represents a potentially modifiable factor that is associated with reduced SVR rates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

AE	adverse events
CI	confidence interval
HCV	hepatitis C virus
LDV	ledipasvir
OR	odds ratio
PPI	proton pump inhibitor
RBV	ribavirin
SOF	sofosbuvir
SVR	sustained virologic response
SVR12	sustained virologic response 12 weeks post-therapy

References

1. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014; 370:1879–1888. [PubMed: 24720702]
2. American Association for the Study of Liver Disease/ Infectious Disease Society of America. [Accessed October 11, 2016] Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org
3. Gordon SC, Muir AJ, Lim JK, et al. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. J Hepatol. 2015; 62:286–293. [PubMed: 25218788]
4. Sulkowski MS, Vargas HE, Di Bisceglie AM, et al. Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection. Gastroenterology. 2016; 150:419–429. [PubMed: 26497081]
5. Harris P, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42:377–381. [PubMed: 18929686]
6. Firth D. Bias reduction of maximum likelihood estimates. Biometrika. 1993; 80:27–38.
7. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014; 370:1483–1493. [PubMed: 24725238]
8. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014; 383:515–523. [PubMed: 24209977]

9. O'Brien T, Feld J, Kottilil S, et al. No scientific basis to restrict 8 weeks of treatment with ledipasvir/sofosbuvir to patients with hepatitis C virus RNA <6,000,000 IU/mL. Hepatology. 2016; 63:28–30. [PubMed: 26474163]

10. Harvoni package insert. [Accessed July 12, 2016] http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf

11. Reddy KR, Bourliere M, Sulkowski M, et al. Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: an integrated safety and efficacy analysis. Hepatology. 2015; 62:79–86. [PubMed: 25846144]

12. Bourliere M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis. 2015; 15:397–404. [PubMed: 25773757]

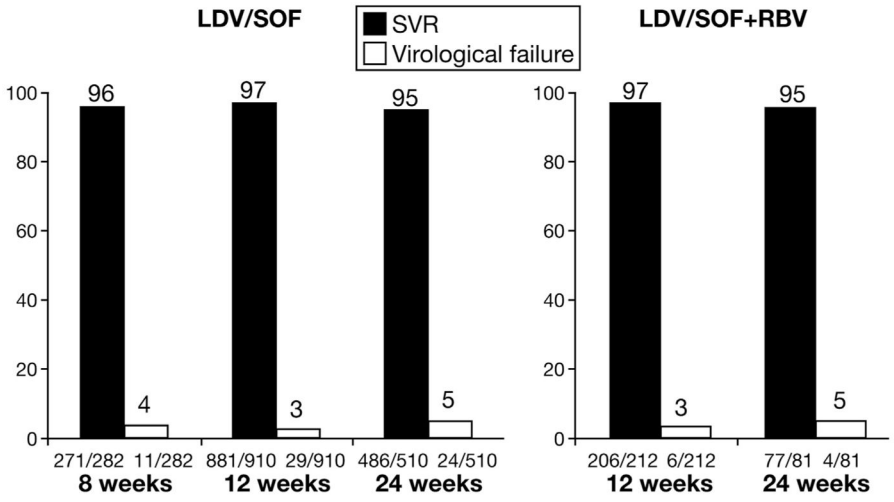

Figure 1.

In the per-protocol population, the SVR12 rate was 96% (95% CI, 95%–97%) among 1788 treated with LDV/SOF and 97% (95% CI, 94%–98%) among 311 treated with LDV/SOF plus RBV. Most of the treatment failures were due to relapse. A total of 7 patients had either virologic breakthrough or failure to achieve unquantifiable HCV RNA on treatment.

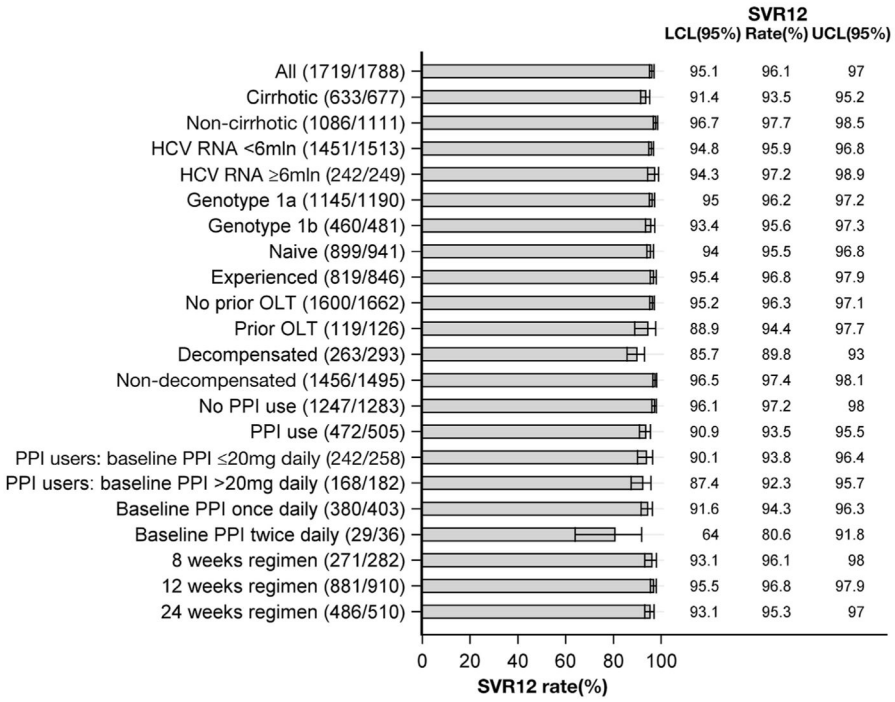

Figure 2.

Only patients who completed treatment with LDV/SOF and have available virologic outcome included (per-protocol population; n = 1788). LCL and UCL are the lower and upper limits of the 95% confidence interval for the SVR12.

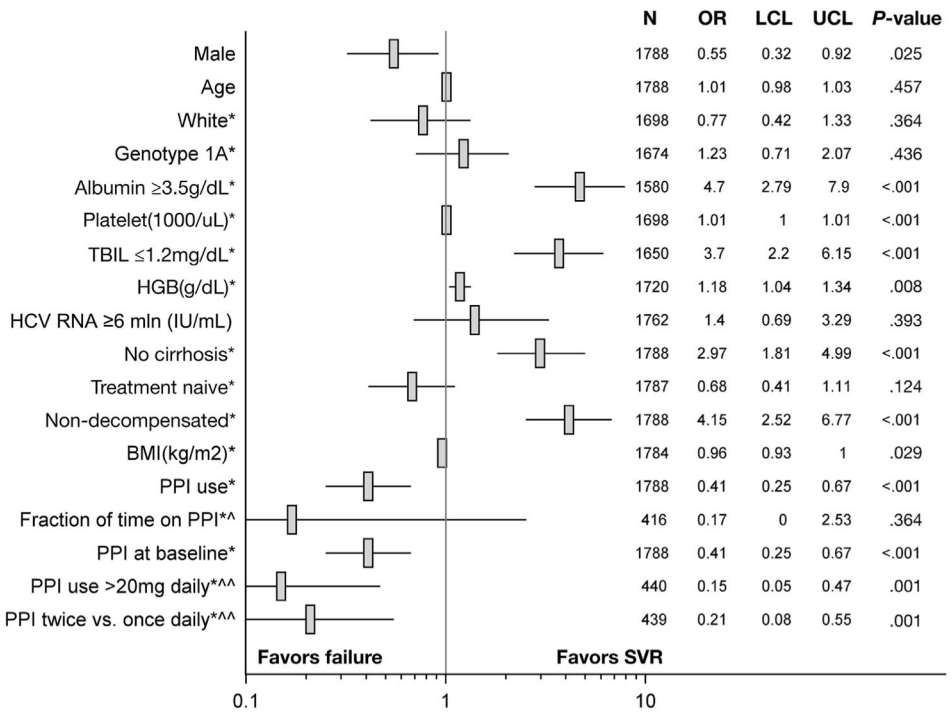

Figure 3.

Only patients who completed treatment with LDV/SOF and have available virologic outcome included (per-protocol population; n = 1788). Each entry in Figure 3 represents a different Firth-penalized logistic regression model for SVR conditional on specified covariables. The entry for “male” represents the effect of being male in a logistic regression model for SVR in which “being male” is the only explanatory covariate. Similarly, the entry “age” represents other univariable model. Subsequent entries (eg, “white”) represent models for the probability of SVR as a function of the variable mentioned (eg, being white) with covariate adjustment for “age” and “sex.” HGB, hemoglobin; LCL, lower limits of the 95% confidence interval for the OR; Nobs, number of observations (patients) contributing data to the fitted model; this number varies due to missing values in the baseline covariables; TBIL, total bilirubin; UCL, upper limits of the 95% confidence interval for the OR.

Table 1

Baseline Characteristics of Patients Treated With Ledipasvir/Sofosbuvir With/Without Ribavirin[a]

Characteristic	LDV/SOF (n = 1927)	LDV/SOF + RBV (n = 328)	Total (n = 2255)
Male, n (%)	1124 (58)	234 (71)	1358 (60)
Age, *y*, median (range)	60 (18–87)	61 (22–85)	60 (18–87)
Race, n (%)			
White	1266 (66)	254 (77)	1520 (67)
Black	522 (27)	36 (11)	558 (25)
Other/not reported	139 (7)	38 (12)	177 (8)
Treatment status, n (%)			
Naïve	1023 (53)	109 (33)	1132 (50)
Experienced	903 (47)	219 (67)	1122 (50)
DAA-experienced	250 (13)	56 (17)	306 (14)
Cirrhosis, n (%)	728 (38)	189 (58)	917 (41)
Decompensated, n (%)	318 (17)	96 (29)	414 (18)
Liver transplant, n (%)	128 (7)	157 (48)	285 (13)
HIV-infected, n (%)	83 (4)	8 (2)	91 (4)
PPI use, n (%)	550 (29)	122 (37)	672 (30)
PPI use at baseline, n (%)	506 (26)	115 (35)	621 (28)
Among PPI users, n (%)			
PPI use for the entire treatment	396/444 (89)	90/109 (83)	486/553 (89)
Baseline PPI use ≤20 mg daily	258/440 (59)	64/109 (59)	322/549 (59)
Genotype, n (%)			
1A	1290 (67)	207 (63)	1497 (66)
1B	514 (27)	94 (29)	608 (27)
Other/unknown	123 (6)	27 (8)	150 (6)
HCV RNA, log_{10} *IU/mL*, median (range)[b]	6.2 (0–8)	6.3 (0–8)	6.2 (0–8)
HCV RNA ≥6 million IU/mL, n (%)	263 (14)	65 (20)	328 (15)
Albumin, *g/dL*, median (range)	4.0 (1.0–6.9)	3.9 (1.7–4.9)	4.0 (1.0–6.9)
Albumin ≥3.5 g/dL, n (%)	1411 (73)	216 (66)	1627 (72)
Total bilirubin, *g/dL*, median (range)	0.6 (0.1–9.3)	0.8 (0.3–27.1)	0.7 (0.1–27.1)
Total bilirubin ≤1.2 g/dL, n (%)	1500 (78)	226 (69)	1726 (77)
Platelets, × $10^3/\mu L$, median (range)	176 (6–647)	133 (26–545)	169 (6–647)
MELD, median (range), cirrhotics only	9 (6–28)	9 (6–21)	9 (6–28)

DAA, direct-acting antiviral; HIV, human immunodeficiency virus; MELD, Model for End-Stage Liver Disease.

[a] Completed treatment as of December 31, 2015 and have available outcomes (evaluable population). Includes patients treated for any duration of treatment. Patients who prematurely discontinued or were lost to follow-up are excluded.

[b] HCV RNA log of 0 represents patients with detectable but not quantifiable results.

Table 2

Safety Profile of Patients Treated with Ledipasvir/Sofosbuvir[a]

Variable	SOF/LDV, n (%) (n = 1927)	LDV/SOF + RBV, n (%) (n = 328)	Total, n (%) (n = 2255)
Total patients with any AE	1217 (63)	280 (85)	1497 (66)
Fatigue	436 (22.6)	121 (36.9)	557 (24.7)
Headache	409 (21.2)	76 (23.2)	485 (21.5)
Infections and infestations	159 (8.3)	43 (13.1)	202 (9.0)
Nausea	155 (8.0)	43 (13.1)	198 (8.8)
Diarrhea	123 (6.4)	38 (11.6)	161 (7.1)
Insomnia	117 (6.1)	29 (8.8)	146 (6.5)
Anemia	11 (0.6)	93 (28.3)	104 (4.6)
Dizziness	82 (4.3)	20 (6.1)	102 (4.5)
Influenza-like illness	66 (3.4)	27 (8.2)	93 (4.1)
Dyspnea	54 (2.8)	35 (10.7)	89 (3.9)
Rash	50 (2.6)	35 (10.7)	85 (3.8)
Cough	53 (2.8)	23 (7.0)	76 (3.4)
Pruritus	36 (1.9)	31 (9.5)	67 (3.0)
Decreased appetite	34 (1.8)	24 (7.3)	58 (2.6)
Irritability	19 (1.0)	22 (6.7)	41 (1.8)
Cardiac disorders	36 (1.9)	14 (4.3)	50 (2.2)
Palpitations	11 (0.6)	6 (1.8)	17 (0.8)
Tachycardia	10 (0.5)	3 (0.9)	13 (0.6)
Angina	4 (0.2)	1 (0.3)	5 (0.2)
Cardiac failure congestive	4 (0.2)	0 (0.0)	4 (0.2)
Arrhythmia	3 (0.2)	0 (0.0)	3 (0.1)
Atrial fibrillation	2 (0.1)	0 (0.0)	2 (0.1)
Bradycardia	2 (0.1)	0 (0.0)	2 (0.1)
Coronary artery disease	2 (0.1)	0 (0.0)	2 (0.1)
Cardiac flutter	0 (0.0)	1 (0.3)	1 (0.0)
Cardiovascular disorder	1 (0.1)	0 (0.0)	1 (0.0)
Myocardial infarction	0 (0.0)	1 (0.3)	1 (0.0)
Pulseless electrical activity	1 (0.1)	0 (0.0)	1 (0.0)
Sick sinus syndrome	0 (0.0)	1 (0.3)	1 (0.0)
Supraventricular tachycardia	0 (0.0)	1 (0.3)	1 (0.0)
Total patients with serious AE	105 (5)	29 (9)	134 (6)
Infections and infestations	24 (1.2)	8 (2.4)	32 (1.4)
Gastrointestinal hemorrhage	6 (0.3)	1 (0.3)	7 (0.3)
Renal failure acute	5 (0.3)	1 (0.3)	6 (0.3)
Anemia	0 (0.0)	5 (1.5)	5 (0.2)
Cardiac failure congestive	4 (0.2)	0 (0.0)	4 (0.2)
Abdominal pain	3 (0.2)	0 (0.0)	3 (0.1)
Pancytopenia	1 (0.1)	1 (0.3)	2 (0.1)

Variable	SOF/LDV, n (%) (n = 1927)	LDV/SOF + RBV, n (%) (n = 328)	Total, n (%) (n = 2255)
Angina pectoris	1 (0.1)	1 (0.3)	2 (0.1)
Generalized edema	1 (0.1)	1 (0.3)	2 (0.1)
Pyrexia	1 (0.1)	1 (0.3)	2 (0.1)
Kidney transplant rejection	1 (0.1)	1 (0.3)	2 (0.1)
Dehydration	2 (0.1)	0 (0.0)	2 (0.1)
Gout	2 (0.1)	0 (0.0)	2 (0.1)
Hyperglycemia	1 (0.1)	1 (0.3)	2 (0.1)
Arthralgia	2 (0.1)	0 (0.0)	2 (0.1)
Convulsion	2 (0.1)	0 (0.0)	2 (0.1)
Headache	2 (0.1)	0 (0.0)	2 (0.1)
COPD	1 (0.1)	1 (0.3)	2 (0.1)
Hepatobiliary serious AEs			
Hepatic encephalopathy	15 (0.8)	5 (1.5)	20 (1.0)
Hepatocellular carcinoma	1 (0.1)	1 (0.3)	2 (0.1)
Bile duct stenosis	2 (0.1)	0 (0.0)	2 (0.1)
Cholecystitis	2 (0.1)	0 (0.0)	2 (0.1)
Hepatic cancer recurrent	1 (0.1)	0 (0.0)	1 (0.0)
Cholangitis	0 (0.0)	1 (0.3)	1 (0.0)
Cholelithiasis	0 (0.0)	1 (0.3)	1 (0.0)
Hepatic lesion	1 (0.1)	0 (0.0)	1 (0.0)
Jaundice	0 (0.0)	1 (0.3)	1 (0.0)
Transaminases increased	1 (0.1)	0 (0.0)	1 (0.0)

COPD, chronic obstructive pulmonary disease.

[a]AEs and serious AEs reported for patients who completed treatment as of December 31, 2015 and have available outcomes. Includes patients treated for any duration of treatment. Patients who prematurely discontinued or were lost to follow-up are excluded. Serious AEs reported only serious AEs with 2 or more occurrences as well as any hepatobiliary serious AE.