



Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study

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Summary

Background Data about the response of hepatitis C virus (HCV) genotype 5 to approved and experimental treatment regimens are scarce. We assessed the efficacy and safety of combination therapy with the NS5A inhibitor ledipasvir and the NS5B polymerase inhibitor sofosbuvir in patients with HCV genotype 5.

Methods We did this open-label, multicentre, single-arm, phase 2 trial at five hospitals in France. Eligible patients were at least 18 years old and had chronic infection with HCV genotype 5, with plasma HCV RNA of at least 10 000 IU/mL. We used BLAST analyses of NS5B partial sequences to establish the genotype and subtype at screening. Patients were given a fixed-dose combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir orally once per day for 12 weeks. The primary endpoint was the proportion of patients with a sustained viral response, defined as HCV RNA concentration less than 15 IU/mL at 12 weeks after the end of treatment (SVR12). We analysed efficacy and safety in all patients who received at least one dose of ledipasvir-sofosbuvir. This trial is registered with EudraCT, number 2013-003978-27, and with ClinicalTrials.gov, number NCT02081079.

Findings From March 7 to June 10, 2014, we recruited 41 patients, including 21 who were treatment naive and 20 who were treatment experienced. All patients were of white ethnic origins. All 41 patients who started treatment completed the full 12 weeks of treatment and had undetectable HCV RNA at their final treatment visit. In the overall study population, 39 (95%, 95% CI 83–99) of 41 patients achieved SVR12. SVR12 was achieved by 20 (95%, 76–100) of the 21 patients who were treatment naive and 19 (95%, 75–100) of the 20 patients who were treatment experienced. Eight (89%) of nine patients with cirrhosis achieved SVR12, whereas 31 (97%) of the 32 patients without cirrhosis achieved SVR12. The two patients who did not reach SVR12 both had *IL28B* TT genotype and had viral relapse within 4 weeks of the end of treatment. The most common adverse events were asthenia (16 [39%] patients), headache (11 [27%] patients), and fatigue (four [10%] patients). One patient had a serious adverse event, worsening depression, which we judged to be unrelated to study treatment.

Interpretation The oral regimen of ledipasvir-sofosbuvir is an effective and well-tolerated treatment for patients with HCV genotype 5 infection who are treatment naive or treatment experienced.

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Introduction

Hepatitis C virus (HCV) genotype 5 accounts for about 1.4 million cases of HCV infection globally.¹ Although more than 80% of cases occur in southern and eastern sub-Saharan Africa,¹ clusters of HCV genotype 5 exist in regions of Belgium, France, Spain, Greece, and Syria.^{2,3} For example, in France, the overall prevalence of HCV genotype 5 infection is estimated to be 1–3% of HCV infections,⁴ but in the Clermont-Ferrand area of central France, 14% of patients infected with HCV were identified as having genotype 5 infection.^{5,6} In this area of central France, HCV genotype 5 was spread locally by unsafe injections before 1972 and more widely by transfusions, with the eventual infection of hundreds of patients. Although data about the natural history of HCV genotype 5 infection are scarce, some evidence suggests that patients with genotype 5 HCV are generally older than are those with other genotypes of HCV, usually have high viral loads, and frequently have cirrhosis.^{2–4,7}

The eradication of HCV with antiviral drugs reduces liver-related complications and improves short-term survival.^{8,9} Patients with HCV genotype 5 have had relatively low rates of response to pegylated interferon- α and ribavirin, with about 60% achieving sustained virological response (SVR) after 48 weeks of therapy.¹⁰ The development of antivirals that directly target HCV (ie, directly acting antivirals) has increased available treatment options and success of treatment for many patients with chronic HCV,^{11–13} but these new regimens have been assessed in very few patients with HCV genotype 5. Provision of an all-oral regimen for HCV genotype 5 infection could expand access to treatment globally, especially in regions with limited resources such as Africa, where the most genotype 5 HCV infections are found.

Combination therapy with the NS5A inhibitor ledipasvir and the NS5B polymerase inhibitor sofosbuvir shows efficacy in several HCV genotypes. In patients

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Research in context

Evidence before this study

In April, 2013, we did a search of PubMed for all papers published in English between January, 1990, and April, 2013, using the keywords "HCV genotype 5", "HCV genotype 5 treatment", and "HCV genotype 5 epidemiology". This study was designed in the first half of 2013, before any all-oral regimens for hepatitis C virus (HCV) infection had been approved. At the time of study design, many reports had described the use of directly acting antivirals as part of interferon-based or all-oral regimens for HCV, but very few patients with HCV genotype 5 were included. The recommendation in the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America and the European Association for the Study of the Liver (EASL) guidelines for patients with HCV genotype 5 infection to receive 12 weeks of triple therapy with sofosbuvir, ribavirin, and pegylated interferon-alfa was based on data from a single patient with HCV genotype 5 in the NEUTRINO trial.

Added value of this study

To our knowledge, this study is the first to assess a treatment regimen consisting entirely of directly acting antivirals in patients with HCV genotype 5 infection. 12 weeks of a fixed-dose combination tablet of ledipasvir-sofosbuvir once per day resulted in sustained viral responses in 39 (95%) of 41 patients at 12 weeks after the end of treatment. Treatment was equally successful irrespective of whether patients were treatment naive or treatment experienced.

Implications of all the available evidence

Based on the results of this study, the AASLD treatment guidelines have been modified such that ledipasvir-sofosbuvir for 12 weeks is now the recommended treatment for patients with HCV genotype 5 infection who are treatment naive or treatment experienced. EASL treatment guidelines also recommend treatment with ledipasvir-sofosbuvir for 12 weeks in patients with HCV genotype 5 infection.

with HCV genotype 1 infection in the ION-1 and ION-2 studies, treatment with ledipasvir-sofosbuvir for 12 weeks resulted in SVR in 99% of patients who were treatment naive and 94% of patients who were treatment experienced.^{14,15} In the SYNERGY study of 21 patients with HCV genotype 4 infection who were treatment naive or experienced, 12 weeks of ledipasvir-sofosbuvir resulted in SVR at 12 weeks after treatment in 95% of patients.¹⁶ Furthermore, in the ELECTRON2 study, 24 (96%) of 25 patients with HCV genotype 6 infection achieved SVR after 12 weeks of ledipasvir-sofosbuvir.¹⁷ However, no data have been available about the efficacy and safety of all-oral HCV regimens for patients with HCV genotype 5 infection. Consequently, we did a trial to assess the efficacy and safety of a fixed-dose combination of ledipasvir-sofosbuvir in patients with HCV genotype 5.

Methods

Study design and participants

This was an open-label, multicentre, single-arm, phase 2 trial. Patients with genotype 5 HCV infection were enrolled and treated at five hospitals in France (two in suburban Paris, two in central France, and one in the southwest). The study protocol was approved by each institution's ethics committee before the start of the study. The study was done in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki.

Study details were posted on ClinicalTrials.gov and patients were referred by their treating physicians. All potentially eligible patients presenting to one of the five hospitals were offered the opportunity to participate and were screened. Eligible patients were at least 18 years old and had chronic infection with HCV genotype 5,

with plasma HCV RNA concentrations of at least 10 000 IU/mL. We used BLAST analyses of *NS5B* partial sequences to establish genotype and subtype at screening, which were confirmed by BLAST analyses of *NS5A* or *NS5B* full-length sequences. Patients could be either HCV treatment naive or treatment experienced. Treatment experience was defined as having received treatment with an interferon-containing regimen, with or without a protease inhibitor. Up to 50% of patients could have compensated cirrhosis, as established by liver biopsy, or by a Fibroscan (Echosens, Paris, France) score of more than 12.5 kPa, or by a FibroTest (BioPredictive SAS, Paris, France) score of more than 0.75 combined with an aspartate aminotransferase (AST)-to-platelet ratio index of more than 2.

Exclusion criteria were body-mass index less than 18 kg/m²; decompensated liver disease; hepatocellular carcinoma; HIV or hepatitis B virus co-infection; creatinine clearance less than 60 mL/min as calculated by the Cockcroft-Gault equation; albumin <30 g/L; international normalised ratio (INR) more than 1.5 times the upper limit of normal (ULN); haemoglobin less than 110 g/L for women and less than 120 g/L for men; platelets less than 50 000/ μ L; direct bilirubin more than 1.5 times the ULN; alanine aminotransferase (ALT) or AST more than ten times the ULN; glycated haemoglobin (HbA_{1c}) more than 10%; history of solid organ transplantation; chronic non-HCV liver disease; malignancy within the 5 years before screening, with the exception of cancers cured by surgical resection; significant pulmonary or cardiac disease; porphyria; screening electrocardiogram (ECG) with clinically significant abnormalities; psychiatric hospital admission, suicide attempt, or a period of disability as a result of a psychiatric disorder within the past 2 years; gastrointestinal disorder or post-operative

disorder that could interfere with study drug absorption; significant drug allergy; chronic use of systemically administered immunosuppressive agents; or clinically relevant drug or alcohol misuse within the previous 12 months. Women who were either pregnant or nursing were also excluded from participation. *IL28B* genotype was established by use of PCR amplification and sequencing of the rs12979860 single nucleotide polymorphism. All patients provided written informed consent before undergoing any study-related procedures.

Procedures

Patients received a fixed-dose combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir orally once per day for 12 weeks. On-treatment adherence was measured by pill counts at each visit after day 1. Treatment would be stopped for patients with confirmed HCV RNA greater than or equal to the lower limit of quantification after two consecutive measures of HCV RNA of less than the lower limit of quantification, confirmed HCV RNA more than 1 log₁₀ increase from the lowest measure, or HCV RNA greater than or equal to the lower limit of quantification through 8 weeks of treatment.

Blood samples for the assessment of plasma HCV RNA concentrations were drawn at screening; on day 1 of treatment; at weeks 1, 2, 4, 8, and 12 of treatment; and at follow-up weeks 4, 12, and 24 (week 24 follow-up not reported). We analysed plasma HCV RNA by use of the COBAS Ampliprep/COBAS TaqMan HCV Quantitative Test version 2.0 (Roche Molecular Systems, Branchburg, NJ, USA), which has a lower limit of quantification of 15 IU/mL.

We attempted deep sequencing of the HCV *NS5A* and *NS5B* genes for all patients at baseline and for patients with viral relapse, at the time of relapse. The full-length HCV *NS5A* and *NS5B* coding regions were amplified and deep sequenced with the illumine MiSeq deep sequencing platform (Illumina, San Diego, CA, USA) by DDL Diagnostic Laboratory (Rijswijk, Netherlands). We did analysis to establish the presence of resistance-associated variants at baseline and at relapse by use of deep sequencing with a 1% cutoff for both *NS5A* and *NS5B*.

Outcomes

The primary efficacy endpoint was the proportion of patients with SVR12, defined as HCV RNA concentration less than the lower limit of quantification (15 IU/mL) at 12 weeks after the end of treatment with the study drug. Patients with missing follow-up week 12 data could be judged as achieving SVR12 if the follow-up week 12 visit was bracketed by successes; if follow-up week 4 data were also missing, the end-of-treatment visit was deemed the preceding visit for the efficacy analysis. Secondary efficacy endpoints included the proportions of patients with SVR at 4 weeks' post treatment, viral breakthrough, or viral relapse.

We collected safety data during treatment and for 4 weeks' post treatment. These data included adverse events, clinical laboratory tests, vital signs, and, on day 1 and week 12 of treatment, physical examinations. We also recorded use of concomitant drugs. We did not do safety assessments, apart from collection of serious adverse events, after the 4 weeks' post-treatment visit. Treatment-emergent clinical and laboratory adverse events were summarised in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. Adverse events were graded as being mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4).

Statistical analysis

We aimed to enrol about 40 patients, with half being treatment naive and half treatment experienced.

In the primary efficacy analysis, we calculated the proportion of patients with SVR12 with a two-sided 95% CI by use of the Clopper-Pearson method. Before study initiation, we calculated two-sided 95% exact CIs for various SVR12 rates in view of subgroup sizes of 20 patients: for SVR rates of 85% the 95% exact CI was 62–97 and for rates of 90%, the 95% exact CI was 68–99. No inferential statistics or statistical comparisons were planned for efficacy endpoints. We analysed efficacy and safety in all patients who received at least one dose of ledipasvir-sofosbuvir.

All analyses were done with SAS (version 9.2). This trial is registered with EudraCT, number 2013-003978-27, and ClinicalTrials.gov, number NCT02081079.

Role of the funding source

The funder collected the data, monitored the conduct of the study, and did the statistical analyses. The investigators, participating institutions, and funder agreed to maintain confidentiality of the data. All authors had access to the data and assume responsibility for the integrity and completeness of the data and analyses

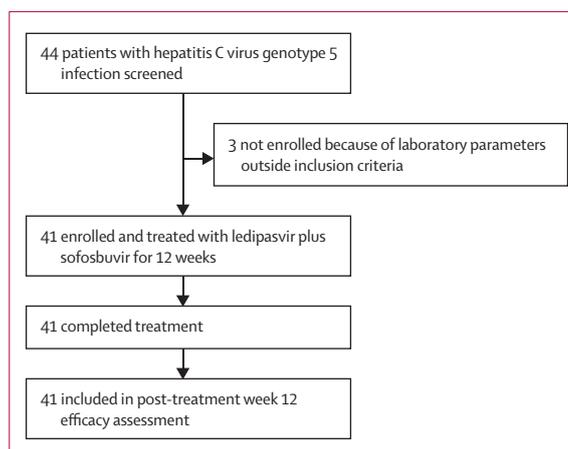


Figure: Trial profile

reported. The first draft of the manuscript was prepared by a professional writer (paid by Gilead Sciences) and the corresponding author, with input from all the authors.

Results

From March 7, to June 10, 2014, we enrolled 41 patients (figure). All patients were white, 21 (51%) were men (table 1), and 39 (95%) self-identified as being white European. Information about the source of HCV

infection was not collected. The numbers of patients who were treatment naive (n=21) and treatment experienced (n=20) were similar. Of the patients who were treatment experienced, six (30%) had cirrhosis, compared with three (14%) of the patients who were treatment naive. For 39 (95%) patients, the presence or absence of cirrhosis was established with Fibroscan (liver biopsy and FibroTest/APRI were each used for one patient). No patients had previously received treatment with a protease inhibitor. All patients completed 12 weeks of treatment. One patient did not complete the week 4 and 12 follow-up visits, but returned for the 24-week follow-up visit. Of the 39 patients who had successful sequencing data, eight (21%) had HCV NS5A resistance-associated variants at baseline: Q30R/L (n=2, at 2.5% and 3.9% of viral population), L31M/F (n=4, 29.5% to >99% of viral population), and P58S (n=2, 9.9% and 94.6% of viral population). Of these 39 patients, at baseline we detected the NS5B variant N142T (1.1% to 19.2% of viral population) in seven (18%) patients and M289I (7.6% and 98.3% of viral population) in two (5%) patients.

Of the 41 patients who started treatment with ledipasvir-sofosbuvir, 39 (95%, 95% CI 83–99) reached the primary endpoint of SVR12. During treatment, all 41 patients had HCV RNA less than the lower limit of quantification by week 8 and HCV RNA was not detected at the final

	Treatment naive (n=21)	Treatment experienced (n=20)
Age (years)	61 (10.4)	64 (8.6)
Male	11 (52%)	10 (50%)
Ethnic origin		
White	21 (100%)	20 (100%)
European	20 (95%)	19 (95%)
Middle Eastern or North African	1 (5%)	1 (5%)
Body-mass index <30 kg/m ²	21 (100%)	17 (85%)
HCV RNA (log ₁₀ IU/mL)	6.2 (0.48)	6.6 (0.39)
HCV genotype subtype		
5a	20 (95%)	20 (100%)
Unknown	1 (5%)	0
Previous HCV treatment response		
Relapse/breakthrough	..	14 (70%)
Non-response	..	5 (25%)
Interferon intolerant	..	1 (5%)
IL28B genotype		
CC	13 (62%)	6 (30%)
CT	7 (33%)	11 (55%)
TT	1 (5%)	3 (15%)
Cirrhosis	3 (14%)	6 (30%)
Alanine aminotransferase (U/L)	42 (26–82)	39 (27–101)
Creatinine clearance ^a (mL/min)	85.4 (74.4–92.1)	85.1 (77.7–107.4)

Data are mean (SD), n (%), or median (range). HCV=hepatitis C virus. ^aEstimated with the Cockcroft Gault equation.

Table 1: Patient demographics and baseline characteristics

	Patients (n=41)
Any adverse events	33 (80%)
Serious adverse events	1 (2%)
Adverse events leading to discontinuation	0
Deaths	0
Adverse events in ≥5% of patients	
Asthenia	16 (39%)
Headache	11 (27%)
Fatigue	4 (10%)
Upper abdominal pain	3 (7%)
Arthralgia	3 (7%)
Diarrhoea	3 (7%)
Dizziness	3 (7%)
Musculoskeletal pain	3 (7%)
Myalgia	3 (7%)
Nasopharyngitis	3 (7%)
Urinary tract infection	3 (7%)
Cough	2 (5%)
Serious adverse events	
Depression	1 (2%)
Laboratory abnormalities	
Total bilirubin >1.0–1.5 ULN	4 (10%)
Haemoglobin 100–109 g/dL	1 (2%)
Lipase >1.5–3.0 ULN	1 (2%)
Platelets 100 000/μL to <125 000/μL	1 (2%)

ULN=upper limit of normal.

Table 3: Treatment-emergent adverse events and laboratory abnormalities

	Treatment naive (n=21)	Treatment experienced (n=20)	Total (N=41)
Viral response at final on-treatment visit*	21 (100%, 84–100)	20 (100%, 83–100)	41 (100%, 91–100)
SVR after treatment			
Week 4	20 (95%, 76–100)	19 (95%, 75–100)	39 (95%, 83–99)
Week 12	20 (95%, 76–100)	19 (95%, 75–100)	39 (95%, 83–99)
On-treatment relapse	0	0	0
Post-treatment relapse	1 (5%)	1 (5%)	2 (5%)

Data are n (%; 95% CI) or n (%). Viral response was defined as HCV RNA <15 IU/mL. HCV=hepatitis C virus. HCV=hepatitis C virus. SVR=sustained viral response. *Final visit was week 12 unless patients missed treatment at week 12, in which case, the latest visit was used.

Table 2: Viral response

treatment visit. Equal proportions of patients who were treatment naive (20 [95%, 76–100] patients) and treatment experienced (19 [95%, 75–100] patients) achieved SVR12. Of the nine patients with cirrhosis, eight (89%) achieved SVR12. Seven of eight patients who had an NS5A resistance-associated variant at baseline and all nine patients with the NS5B resistance-associated variants N142T or M289I at baseline achieved SVR12.

Two patients had viral relapse by post-treatment week 4 (table 2). Both patients had HCV RNA less than the lower limit of quantitation at week 1 and undetectable from week 2 to the end of treatment. Of these two patients, one was a 72-year-old man who was treatment-experienced (having had a partial response) and had an *IL28B* TT genotype, cirrhosis, and a baseline HCV RNA concentration of 1700000 IU/mL. This patient had the NS5A resistance-associated variant L31M at greater than 99% of viral population at baseline, which was retained with no additional NS5A resistance-associated variant at the time of relapse. This patient also had emergent NS5B S282T (2% viral population) and M289I (16% viral population) resistance-associated variants at relapse. The other patient who had relapse was a 56-year-old woman who was treatment naive, had no cirrhosis, and had the *IL28B* TT genotype and a baseline HCV RNA concentration of 180000 IU/mL. The genotype 5 subtype could not be established for this patient. For this patient, both baseline and post-treatment full-length amplification of NS5A and NS5B failed; population sequencing of a partial NS5B fragment showed no S282T at viral relapse.

The most common adverse events were asthenia in 16 (39%) patients, headache in 11 (27%) patients, and fatigue in four (10%) patients (table 3). No patients discontinued treatment because of an adverse event. All adverse events were mild or moderate in severity except for one grade 3 serious adverse event of worsening depression, which we judged to be unrelated to study treatment. We detected no grade 3 or 4 laboratory abnormalities.

Discussion

This prospective, open-label study is the first to assess a regimen consisting of only directly acting antivirals in patients with HCV genotype 5 infection. The study population of 41 patients is large for a study of HCV genotype 5, which is rare worldwide but is more concentrated in regions of Africa and Europe. All patients in this study were enrolled in France, including 17 (41%) in Clermont-Ferrand, which has a documented cluster of mainly iatrogenic HCV genotype 5 infections.^{5,6}

In this study, a fixed-dose combination regimen with ledipasvir-sofosbuvir once per day for 12 weeks resulted in SVR in 39 (95%) of 41 patients. Patients who were treatment naive or treatment experienced were equally likely to reach SVR. Because of the high level of success, it is not clear which, if any, baseline characteristics might have predicted outcome. Only two patients did not

achieve the primary endpoint. Both had the *IL28B* TT genotype, but otherwise shared few clinical or demographic characteristics. Eight (89%) of nine patients with cirrhosis achieved SVR.

Of the 39 patients with sequencing data available, eight (21%) patients had HCV with NS5A resistance-associated variants at baseline. Only one of these patients did not reach SVR12; this patient did not develop any new NS5A resistance-associated variants at viral relapse. We detected the baseline NS5B variants N142T or M289I in nine of 39 patients, and all nine reached SVR12. Taken together, the presence of NS5A resistance-associated variants and NS5B N142T and M289I had no meaningful effect on the treatment outcome for the ledipasvir-sofosbuvir regimen. Of the two patients with viral relapse, the NS5B variants S282T and M289I emerged at viral relapse in one patient who also had the NS5A resistance-associated variant L31M at baseline.

Treatment with ledipasvir-sofosbuvir for 12 weeks was mostly well tolerated. No patients discontinued treatment because of an adverse event. Only one serious adverse event, worsening depression, was reported, and we deemed it to be unrelated to study treatment. Few clinical laboratory abnormalities were reported and all were grade 1 or 2. These results are consistent with the safety profile reported in phase 3 studies of ledipasvir-sofosbuvir for patients with HCV genotype 1 infection.^{14,15}

Both patients who failed treatment in this study had the *IL28B* TT genotype. Given that only four patients with the TT genotype were enrolled, this finding is suggestive, but the sample size is too small for any definitive conclusions to be drawn. An association between non-CC *IL28B* genotypes and reduced response to treatment has previously been reported only in patients receiving interferon-based regimens; analysis of data from the ION phase 3 studies in patients with HCV genotype 1 infection has not revealed any association between *IL28B* genotype and response to treatment with ledipasvir-sofosbuvir.^{14,15} In the small amount of clinical data available for patients with HCV genotype 5 infection, no significant association between *IL28B* TT genotype and response has been reported, even in patients receiving interferon-based regimens.^{18,19} Nevertheless, the possible effect of *IL28B* genotype on response to ledipasvir-sofosbuvir in patients with HCV genotype 5 infection clearly warrants further investigation in a larger trial.

The C-SCAPE trial of the NS3/4A protease inhibitor grazoprevir and the NS5A inhibitor elbasvir with or without ribavirin included eight patients with HCV genotype 5 who had failed previous therapy that included a directly acting antiviral.²⁰ SVR12 was reached by all four patients who received triple therapy with grazoprevir, elbasvir, and ribavirin, but only one of four patients who received the combination of only the directly acting antivirals grazoprevir and elbasvir. Because the number of patients with HCV genotype 5 was small and all had failed previous therapy, the results from C-SCAPE are

not directly comparable with those of our study, but do suggest that ribavirin might be needed to ensure success for grazoprevir and elbasvir in patients with HCV genotype 5 infection.

Limitations of this study include the relatively small number of patients, despite it being, to our knowledge, the largest group of patients with HCV genotype 5 infection ever assessed for treatment response with a directly acting antiviral and one of the largest groups of patients with HCV genotype 5 infection included in any assessment of treatment response. It is also possible that the patients enrolled in this study might not be broadly representative of patients with HCV genotype 5 infection. All were white and were recruited in France, with the majority from one region of central France, whereas most patients with HCV genotype 5 are from sub-Saharan Africa. Although we cannot generalise our results on the basis of this small, unrepresentative sample, HCV genotype 5 is highly conserved, with only one subtype, 5a, identified so far.³ The absence of diversity suggests that sofosbuvir and ledipasvir would be similarly effective in other populations with HCV genotype 5a worldwide.

In conclusion, in this small, open-label study, 12 weeks of treatment with ledipasvir-sofosbuvir resulted in a high proportion of individuals achieving SVR in patients with HCV genotype 5 infection, irrespective of previous treatment experience or the presence of cirrhosis. This all-oral and ribavirin-free, fixed-dose regimen of ledipasvir-sofosbuvir might represent a substantial advance in treatment for patients with HCV genotype 5, pending confirmation in a larger trial.

Contributors

VL-R, AA, PSP, TA, and KK contributed to the study design. AA, TA, SM, DS, and VL-R were the study investigators. All authors contributed to the data interpretation and writing and review of the report.

Declaration of interests

AA has received speaking and teaching fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, and Merck Sharp & Dohme (MSD); grant and research support from Abbvie, Bristol-Myers Squibb, Gilead Sciences, and MSD; and has served on advisory boards for Abbvie, Bristol-Myers Squibb, Gilead Sciences, and MSD. VL-R has received speaking and teaching fees from Roche, Merck/Schering Plough, Janssen Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, and Abbvie; grant and research support from Roche and Bristol-Myers Squibb; and has served on advisory boards for Roche, Gilead Sciences, Merck/Schering Plough, Bristol-Myers Squibb, and Abbvie. TA has received speaking fees and is an investigator for Gilead Sciences, AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen Pharmaceuticals, Roche, and Merck. KK, DJ, HM, and PSP are employees of Gilead Sciences and hold stock interest in the company. DS has received consulting fees from Astellas, Gilead, Bristol-Myers Squibb, LFB, MSD, Novartis, Roche, Biotest, and Abbvie. SM has received personal fees from Gilead, Bristol-Myers Squibb, Janssen, Abbvie, and Roche.

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