Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study

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Summary

Background Early treatment of acute hepatitis C virus (HCV) infection with interferon alfa is highly effective, but can be associated with frequent side-effects. We investigated the safety and efficacy of an interferon-free regimen for treatment of acute HCV infection.

Methods In this prospective, open-label, multicentre, single-arm pilot study, we enrolled adults (≥18 years) with acute HCV genotype 1 monoinfection from ten centres in Germany. Patients were given ledipasvir (90 mg) plus sofosbuvir (400 mg) as a fixed-dose combination tablet once daily for 6 weeks. The primary efficacy outcome was the proportion of patients with sustained virological response (defined as undetectable HCV RNA 12 weeks after the end of treatment; other primary outcomes were safety and tolerability of ledipasvir plus sofosbuvir. The primary analysis population consisted of all patients who received at least one dose of study drug. Safety was also assessed in all patients who received at least one dose of the study drug. This trial is registered with ClinicalTrials.gov, number NCT02309918.

Findings Between Nov 19, 2014, and Nov 10, 2015, we enrolled 20 patients. Median HCV RNA viral load at baseline was 4·04 $\log_{10}$ IU/mL (1·71–7·20); 11 patients were infected with HCV genotype 1a and nine patients with genotype 1b. All patients achieved a sustained virological response 12 weeks after the end of treatment (20 [100%] of 20 patients). Treatment was well tolerated; there were no drug-related serious adverse events. Up to 12 weeks after treatment, 22 possible or probable drug-related adverse events were reported. There was one serious adverse event, which was judged unrelated to the study drug; one patient was admitted to hospital for surgery of a ruptured cruciate ligament.

Interpretation Treatment for 6 weeks with ledipasvir plus sofosbuvir was well tolerated and highly effective in patients with acute HCV genotype 1 monoinfection. Short-duration treatment of acute hepatitis C might prevent the spread of HCV in high-risk populations.

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Introduction

Hepatitis C virus (HCV) infection leads to chronic hepatitis C in 50–90% of cases.[1–3] Chronic hepatitis C is one of the main causes of end-stage liver disease and hepatocellular carcinoma. Fortunately, the incidence of acute hepatitis C has declined in recent years; however, new infections still occur. A high incidence of HCV in people who inject drugs has been reported.[1,4] Other risk factors for HCV infection include medical procedures[5,6] and sexual intercourse with people infected with HCV, including HIV-positive and HIV-negative men who have sex with men.[1] Furthermore, new infections are still frequently reported in the absence of classic risk factors.

Historically, acute HCV infection has been treated with pegylated interferon alfa-based therapies. High cure rates have been reported with 12–24 weeks of treatment,[1,6–8] and by contrast with interferon treatment of chronic hepatitis C, ribavirin coadministration was not required in acute hepatitis C in most settings. The previous German Acute HCV trials I–III explored the efficacy of conventional recombinant interferon alfa,[9] use of pegylated interferon alfa,[10] and the strategies of immediate versus delayed treatment of acute hepatitis C.[3] Overall, acute HCV infection was cured by early therapy in 89–98% of patients whereas delayed therapies (ie, >12 weeks after first diagnosis) were also effective but associated with higher rates of loss to follow-up. However, treatment with interferon alfa can lead to frequent and sometimes severe side-effects and many patients cannot be treated with this drug because of contraindications.

Several novel direct-acting antiviral drugs against HCV have been approved during the past 2 years allowing interferon-free therapy of chronic hepatitis C. The required treatment duration for chronic hepatitis C is 12 weeks for most patients.[11] Shorter treatments might be possible for a subgroup of patients with chronic

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See Online for appendix

Research in context

Evidence before the study

Historically, acute hepatitis C virus (HCV) infection has been treated with interferon alfa-based therapies. We searched PubMed with the terms "acute hepatitis C", "antiviral treatment", and "interferon-free treatment" for papers published in English between Jan 1, 1995, and May 9, 2016. Several systematic reviews and published studies identified by this search showed that up to 98% of patients with acute hepatitis C can be treated successfully with 12–24 weeks of interferon alfa-based therapies. This finding is in line with experiences from Germany where treatment of acute hepatitis C with interferon alfa or pegylated interferon alfa has been studied in three consecutive trials since 1996. However, interferon alfa therapy can lead to frequent and sometimes severe side-effects and many patients cannot be treated with interferon alfa because of contraindications. The introduction of several direct-acting antiviral drugs against hepatitis C has revolutionised treatment of chronic hepatitis C. More than 95% of patients with chronic hepatitis C can be cured with 8–24 weeks of therapy. However, interferon-free treatment of acute hepatitis C with direct-acting antiviral drugs against HCV is not well studied. We searched PubMed with the same terms as above, and excluded all studies investigating interferon-based therapies of acute hepatitis C. This search did not identify a single fully published study investigating interferon-free treatment of acute hepatitis C with direct-acting antiviral regimens. It was therefore unknown whether treatment of very early HCV infection could be shortened to 6 weeks. Other questions were whether treatment of patients with severe acute icteric hepatitis C with novel antiviral drugs is safe and whether symptoms of acute hepatitis improve with antiviral therapy.

Added value of this study

To our knowledge, this is the first fully published report of a prospective multicentre study investigating the efficacy and safety of interferon-free and ribavirin-free therapy of acute hepatitis C with direct-acting antivirals against hepatitis C. All patients treated with ledipasvir plus sofosbuvir achieved a sustained virological response 12 weeks after the end of treatment. Treatment was well tolerated; there were no drug-related serious adverse events. Thus, all patients with acute hepatitis C could be cured with only 6 weeks of ledipasvir plus sofosbuvir combination therapy, the treatment was safe even in patients with severe hepatitis and jaundice, and early treatment of acute hepatitis C resulted in rapid improvement of biochemical disease activity and symptoms of hepatitis.

Implications of all the available evidence

In the absence of a vaccine against HCV, early treatment of acute hepatitis C is likely to be needed to prevent the spread of HCV in high-risk populations. Early therapy of acute hepatitis C could also shorten disease duration and reduce infection-associated morbidity. Medical health professionals infected after occupational exposure would also benefit from treatment of acute hepatitis C because they could continue to work. Finally, early shorter treatment of acute hepatitis C could potentially be cost-saving compared with standard therapy of chronic hepatitis C. This approach, however, would require the availability of different package sizes of ledipasvir plus sofosbuvir allowing prescriptions for 6 weeks.

hepatitis C who are non-cirrhotic and have additional favourable response profiles, such as those with a low viral load, women, or individuals with a favourable *IFNL3* genotype (*IFNL4*).[12] Overall, more than 95% of patients with chronic hepatitis C can now be cured with the new treatment options across different stages of liver disease and HCV genotypes.[13]

Interferon-free treatment of acute hepatitis C with direct-acting antiviral drugs against HCV is not well studied. Early treatment of acute hepatitis C could prevent the spread of HCV in high-risk populations and reduce overall costs of antiviral therapies because of shorter treatment durations. However, a potential concern is the use of direct-acting antiviral regimens in patients with jaundice and severe hepatitis, and high concentrations of liver enzymes, because the safety of these therapies has not been established in this context. So far, only preliminary reports of case series or smaller prospective treatment trials exploring interferon-free therapy of acute hepatitis C have been presented during conferences. Different direct-acting antiviral combinations including sofosbuvir plus ribavirin or simeprevir or ledipasvir for various treatment durations (4–12 weeks) were tested in HIV-positive individuals as well as in patients with HCV monoinfection. Investigators of these studies reported HCV cure rates between 77% and 93% for sofosbuvir-based regimens.[14–18] We assessed the efficacy and safety of treatment with ledipasvir plus sofosbuvir as a fixed-dose combination for 6 weeks in patients with acute HCV genotype 1 monoinfection.

Methods

Study design and participants

This investigator-initiated study was designed as a phase 2, national, multicentre, prospective, single-arm pilot study and was coordinated by the HepNet Study-House, a project of the German Liver Foundation, funded by the German Centre for Infection Research (DZIF).

We enrolled patients with acute HCV genotype 1 monoinfection from ten centres in Germany. Detailed inclusion and exclusion criteria and study procedures are listed in the protocol. Briefly, eligible patients were at least 18 years of age, had an HCV RNA viral load of more than 10 000 IU/mL at screening, and acute HCV genotype 1 infection. Acute HCV infection was defined as

either a documented seroconversion to HCV antibody positivity within the 4 months before screening, or known or suspected exposure to HCV within the 4 months before screening with raised alanine aminotransferase concentration more than ten times the upper limit of normal at screening or within a 4-week period before screening. Key exclusion criteria were presence of liver cirrhosis, clinical hepatic decompensation, solid organ transplantation, infection with hepatitis B virus or HIV, use of systematically administered drugs, and clinically significant illness that might interfere with study treatment, assessment, or compliance with the protocol. Other causes of liver disease were excluded by standard clinical and laboratory criteria.

All patients provided written informed consent before enrolling in the study. The study was done in accordance with the Declaration of Helsinki (1996 revision) and other applicable national legislation. The study was approved by the competent authority (BfArM). The reporting ethics committee of Hannover Medical School issued a favourable opinion in collaboration with other participating local ethics committees.

Procedures

Patients were given ledipasvir plus sofosbuvir as a fixed-dose combination tablet, consisting of 90 mg ledipasvir and 400 mg sofosbuvir once daily for 6 weeks.

Study visits occurred at screening, baseline, week 2, week 4, and week 6 of antiviral treatment and 12 weeks and 24 weeks after the end of therapy. At each study visit blood and serum samples were taken and HCV RNA was measured. The HCV Genotype 2.0 Assay (LiPA; Siemens Healthcare, Erlangen, Germany) was used for HCV genotyping.

HCV RNA testing was done with the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test version 2.0 (Roche Diagnostics, Mannheim, Germany) with a lower limit of quantification of 15 IU/mL. Biochemical responses (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase) were assessed by the local laboratory of each centre in serum samples using standard enzymatic assays at 37°C on automated platforms.

Outcomes

The primary efficacy endpoint was the proportion of patients with sustained virological response (defined as undetectable HCV RNA) 12 weeks after the end of treatment with the study drug. Other primary endpoints were safety and tolerability of ledipasvir plus sofosbuvir. Secondary endpoints were durability of response 24 weeks after discontinuation of therapy, HCV RNA kinetics during and after treatment, and emergence of viral resistance to ledipasvir plus sofosbuvir. Safety was assessed via analysis of documented adverse events and serious adverse events. Biochemical responses as determined by alanine aminotransferase concentrations were also assessed in a post-hoc analysis.

Statistical analysis

This study was planned as a pilot trial with 20 patients and under the assumption that the proportion of patients who achieve a response will be close to 100% on the basis of already available studies in chronic hepatitis C.[19] The study will be called successful if the lower boundary of the 95% Wilson CI is more than 80%. With 20 patients, this outcome can only be achieved if all treated patients are responders at the timepoint of the primary assessment. The study has a power of 80% if the true response rate is greater than 98%.

Baseline characteristics are reported as absolute and relative frequencies for categorical data and medians, range, and IQR for continuous data. The primary analysis population consisted of all patients who received at least one dose of study drug. Missing data in the primary endpoint were replaced if the previous and followed planned visit values were non-missing. Sensitivity

For the **trial protocol** see http://www.kompetenznetz-hepatitis.de/projekte/HepNet Study-House/acute-hcv-iv-study" http://www.kompetenznetz-hepatitis.de/projekte/HepNet Study-House/acute-hcv-iv-study

	Patients (n=20)
Men	12 (60%)
Age (years)	49 (23–63; 36–54)
Mean	45·94
>40	14 (70%)
Body-mass index (kg/m²)	25·70 (18·7–32·5; 22·9–27·8)
>25	12 (60%)
HCV genotype	
1a	11 (55%)
1b	9 (45%)
HCV RNA (IU/mL)	11 000* (51–16 000 000*; 140–190 000)
≤50 000	12 (60%)
<15	1 (5%)
Log_{10} HCV RNA (IU/mL)	4·04 (1·71–7·20; 2·15–5·28)*
≤5	14 (70%)
Alanine aminotransaminase (U/L)	225 (32–2716; 71·35–721·80)
Bilirubin (μmol/L)	13·6 (5·13–111·18; 10·18–25·13)
Aspartate aminotransferase (U/L)	76·5 (16·0–1071·0; 34·5–286·5)
γ-glutamyl transferase (U/L)	134·15 (15·0–901·20; 71·50–292·0)
Alkaline phosphatase (U/L)	104 (49–207; 80–138)
IFNL3 genotype (*IFNL4*)	
CC	12 (60%)
CT	6 (30%)
TT	2 (10%)
Risk factors for infection	
Sexual transmission	11 (55%)
Medical procedures or needlestick injury	5 (25%)
Nail treatment	1 (5%)
Unspecified	3 (15%)

Data are n (%) or median (range; IQR), unless otherwise stated. HCV=hepatitis C virus. *Median, range, and IQR calculated from all measured data greater than the lower limit of quantification (<15 IU/mL).

Table 1: **Baseline characteristics**

analyses were done in the per-protocol population (ie, all patients who completed the study in accordance with the study protocol). Safety was assessed in all patients who received at least one dose of study drug. For the primary endpoint, the two-sided 95% Wilson CI for the proportion of participants with sustained virological response 12 weeks after the end of treatment was examined. Secondary endpoints are presented by absolute and relative frequencies and patient profile plots. All analyses were done with SAS version 9.3. This trial is registered with ClinicalTrials.gov, number NCT02309918.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 19, 2014, and Nov 10, 2015, we screened 26 patients with acute hepatitis C at ten centres in Germany. Six patients were ineligible at screening (appendix); three patients had HCV RNA viral load less than 10 000 IU/mL at screening, one patient had hepatitis B virus co-infection, one patient reported uncontrolled drug misuse, and one patient had a raised alanine amino-transferase concentration of less than ten times the upper limit of normal within a 4-week period before screening. 20 eligible patients were enrolled in the trial. The mean time between first diagnosis of acute hepatitis C and start of antiviral therapy was 32·8 days (SD 22·4).

Enrolled patients were predominantly men (60%), had a mean age of 46 years (range 23–63), and most had HCV genotype 1a infection (55%; table 1). The most likely risk factor for infection was sexual transmission in more than half of the patients (11 [55%] patients), including five men who have sex with men. Four (20%) patients were probably infected by medical procedures and one (5%) patient by needlestick injury. Nail treatment as a risk factor was reported by one patient. In three patients (15%), the possible route of infection was unknown. 12 (60%) patients had *IFNL3* genotype (*IFNL4*) CC, six (30%) had *IFNL3* genotype (*IFNL4*) CT, and two (10%) had *IFNL3* genotype (*IFNL4*) TT.

	HCV genotype	HCV RNA (IU/mL)					
		Screening	Baseline	Week 2	Week 4	Week 6	Follow-up week 12
01-01	1a	1 900 000	140	<15	ND	ND	ND
03-01	1a	55 000	51	35	ND	ND	ND
03-02	1a	49 000	1 000 000	<15	<15	ND	ND
03-04	1b	16 000	95 000	ND	ND	ND	ND
04-01	1a	480 000	<15	ND	ND	ND	ND
04-03	1b	930 000	240	<15	ND	ND	ND
04-04	1a	1 100 000	11 000	<15	ND	ND	ND
06-01	1b	14 000	14 000	ND	ND	ND	ND
06-02	1a	36 000	880	ND	<15	ND	ND
08-01	1a	34 000	2500	ND	ND	ND	ND
09-01	1a	2300	53	ND	ND	ND	ND
09-02	1b	1900	21 000	<15	<15	ND	ND
09-03	1a	180 000	89 000	32	<15	ND	ND
12-01	1b	860 000	430 000	ND	ND	ND	ND
16-01	1a	2 100 000	2 800 000	3500	<15	ND	ND
18-02	1b	5 600 000	16 000 000	120	<15	ND	ND
18-03	1b	960 000	130	ND	ND	ND	ND
18-04	1a	18 000	150	<15	ND	ND	ND
19-01	1b	3500	190 000	ND	ND	ND	ND
19-02	1b	7000	96	<15	ND	ND	ND

HCV=hepatitis C virus. ND=not detectable.

Table 2: **Individual HCV RNA results at different timepoints, by patient identification number**

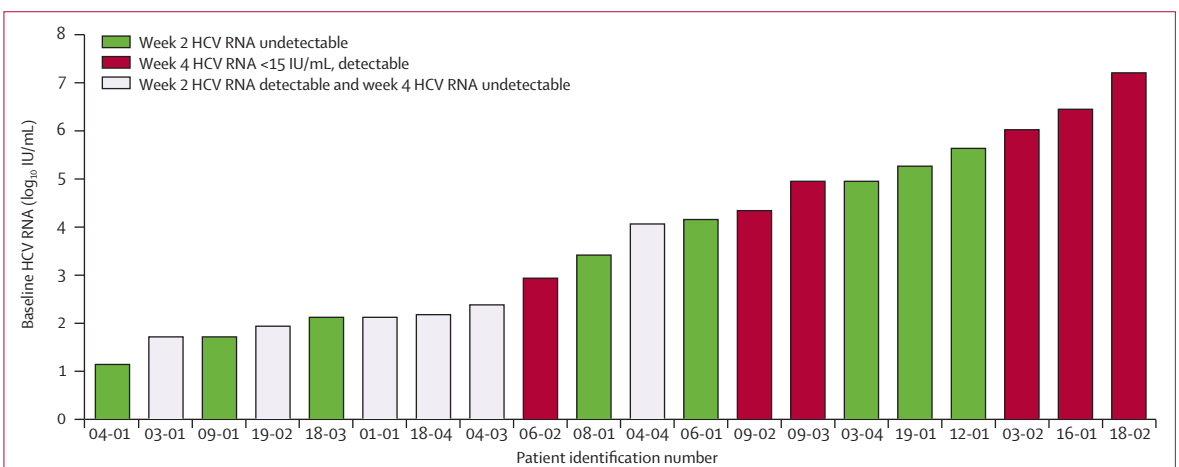

Figure 1: **Baseline HCV RNA viral load and early virological response**

Correlation between baseline hepatitis C virus (HCV) RNA viral load and early virological response as defined by undetectable HCV RNA values at week 2 and correlation between baseline HCV RNA viral load and delayed virological response as defined by detectable HCV RNA at week 4.

Eight (40%) patients had jaundice with bilirubin concentration more than 2·5 times the upper limit of normal at screening. 14 (70%) patients reported fatigue and four (20%) patients had abdominal pain at the time of screening. Overall, 19 patients had symptomatic infection. Two patients had a documented seroconversion, one of whom developed symptoms but had a peak alanine aminotransferase concentration of less than ten times the upper limit of normal, whereas the other patient was asymptomatic but presented with an alanine aminotransferase concentration of more than ten times the upper limit of normal.

Median HCV RNA viral load at baseline in all patients who had a viral load greater than the lower limit of quantification was 4·04 $\log_{10}$ IU/mL (range 1·71–7·20). One patient had a viral load that was less than the lower limit of quantification but with detectable HCV RNA at baseline. After 2 weeks of antiviral treatment, nine patients had undetectable HCV RNA (table 2). At week 4 of antiviral treatment, HCV RNA viral load was less than 15 IU/mL in all 20 patients and detectable but not quantifiable in six patients (predefined secondary endpoint). At the end of therapy (treatment week 6), all 20 patients had undetectable HCV RNA. Similarly, all 20 patients had undetectable HCV RNA 12 weeks after completion of treatment, thus the proportion of patients with a sustained virological response 12 weeks after treatment was 100% (95% Wilson CI 83·89–100). In one patient, measurement of HCV RNA was not done at follow-up week 12, but because HCV RNA was undetectable 3 weeks later and at follow-up week 24, for the analysis HCV RNA was deemed undetectable at follow-up week 12. Data for follow-up week 24 were available for 19 patients. HCV RNA was negative in all patients, thus 95% (95% Wilson CI 76·39–99·11) had a sustained virological response at follow-up week 24 (19 of 20 patients, predefined secondary endpoint; per-protocol analysis 19 [100%; 83·18–100] of 19 patients). Emergence of viral resistance (predefined secondary endpoint) could not be analysed because no virological failure occurred.

There was no correlation between baseline HCV RNA viral load and early virological response as defined by undetectable HCV RNA at week 2 (figure 1). However, patients with a delayed response and detectable HCV RNA at week 4 had higher baseline HCV RNA viral load. Four of the six patients with delayed HCV RNA response were infected with HCV genotype 1a.

A rapid biochemical response was noted: alanine aminotransferase concentrations had reduced to within the normal range in nine (47%) of 19 patients within the first 2 weeks of treatment (value was missing for one patient at week 2), in 16 (80%) of 20 patients within the 6-week treatment period, and in 18 (90%) of 20 patients by follow-up week 12 (figure 2). One of two patients with abnormal alanine aminotransferase concentration had diabetes mellitus and persistently high alanine aminotransferase concentrations between 75 U/L and 102 U/L after week 4 of therapy until follow-up week 24. The other

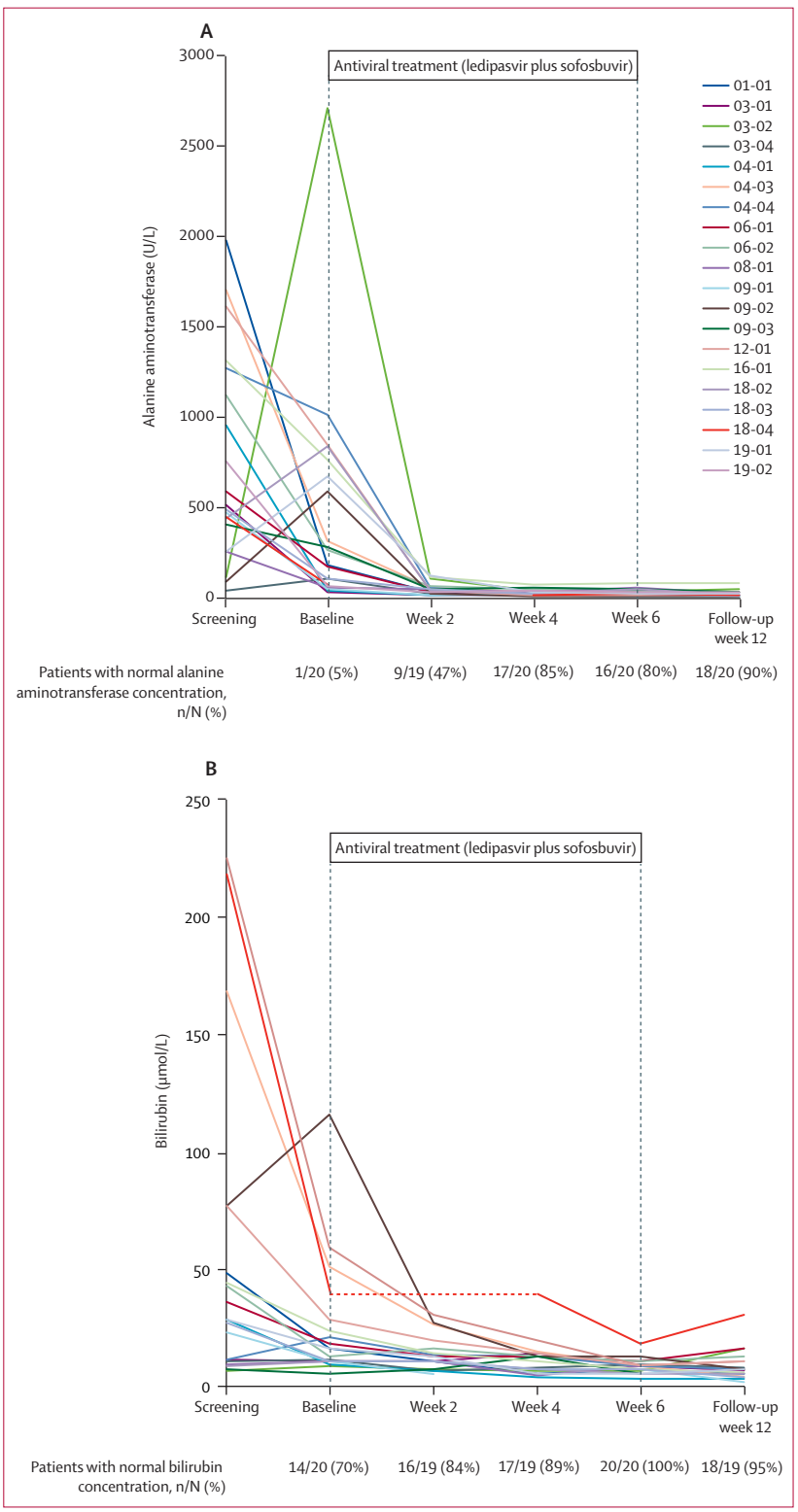

Figure 2: **Biochemical response to antiviral treatment**
Individual concentrations of alanine aminotransferase (A) and bilirubin (B) from each patient at screening, baseline, during antiviral treatment, and up to 12 weeks after the end of treatment are plotted on the graphs. The proportion of patients (for whom we had data) with normal concentrations at baseline, different timepoints during antiviral treatment, and up to 12 weeks after the end of treatment are shown below each graph.

	Number of events (%)
Gastrointestinal symptoms	4 (20%)
Fatigue	3 (15%)
Hair loss	3 (15%)
Headache	2 (10%)
Abdominal pain	2 (10%)
Skin reaction	2 (10%)
Mental problems	2 (10%)
Sleeping disorders	1 (5%)
Mouth burn	1 (5%)
Spleen pain	1 (5%)
Eye twitch	1 (5%)

All drug-related adverse events were possibly or probably related to study treatment; none were definitely related.

***Table* 3: Drug-related adverse events up to 12 weeks after completion of antiviral treatment**

patient had only minimally raised alanine aminotransferase concentration at follow-up week 12 (52 U/L) and normal alanine aminotransferase concentration at the end of treatment and at follow-up weeks 4 and 24. Median bilirubin concentration at baseline was 13·6 µmol/L (range 5·13–111·18). There was a rapid decline in bilirubin concentration between screening and baseline; therefore, only six patients started antiviral treatment with raised bilirubin concentrations. Bilirubin concentration normalised in all 20 patients (100%) during the 6-week treatment period. 18 (95%) of 19 patients had a bilirubin concentration within the normal range at follow-up week 12 (value was missing for one patient; figure 2). Aspartate aminotransferase, alkaline phosphatase, and γ-glutamyl transferase concentrations improved early during the first weeks of treatment (appendix).

All 20 patients completed 6 weeks of antiviral treatment and follow-up week 12. Treatment of symptomatic acute hepatitis C with ledipasvir plus sofosbuvir was well tolerated. 22 possible or probable drug-related adverse events were reported up to follow-up week 12 (table 3). The most frequently reported adverse events were gastrointestinal symptoms (four events [20%]), fatigue (three [15%]), and hair loss (three [15%]). There was one serious adverse event, which was judged unrelated to the study drug; one patient was admitted to hospital for surgery of a ruptured cruciate ligament. There were no major changes during or after therapy in creatinine clearance (appendix), serum lipase concentration, or other biochemical or haematological measures potentially indicating drug toxicities (data not shown).

Discussion

Our results show that a short course of 6 weeks with an interferon-free and ribavirin-free therapy consisting of the direct-acting antiviral drugs ledipasvir and sofosbuvir resulted in a sustained virological response 12 weeks after treatment in all patients with acute HCV genotype 1 monoinfection. Moreover, treatment of patients with jaundice and high concentrations of liver enzymes was not associated with any serious adverse events related to the study drugs but resulted in rapid improvement of symptoms and normalisation of liver enzyme concentrations.

Treatment with ledipasvir plus sofosbuvir led to a rapid decline of HCV RNA in patients with acute hepatitis C. HCV RNA was already undetectable at treatment week 2 in nine of 20 patients. This rapid virological response did not seem to correlate with baseline HCV RNA viral load, suggesting that immune responses might have contributed to early control of HCV infection. However, a delayed virological response indicated by a detectable but not quantifiable HCV RNA test at treatment week 4 was recorded more frequently in patients with a high baseline HCV RNA load. All three patients who had a baseline HCV RNA viral load of more than 10 000 000 IU/mL were not completely negative for HCV RNA after 4 weeks of treatment. Importantly, these results were obtained even though we used the Roche COBAS TaqMan version 2.0 HCV RNA assay, which shows positive results during interferon-free therapy of hepatitis C less frequently than the Abbott RealTime assay (Abbott, Wiesbaden, Germany).[20] Nevertheless, all patients treated in this trial cleared HCV infection despite this prolonged viraemia during therapy. Future studies will need to investigate to what extent immune responses contribute to HCV control in this setting and whether suppression of HCV replication restores immune cell function in acute hepatitis C, which can occur to some extent in chronic hepatitis C.[21–26] This question becomes even more relevant because in a trial in HIV-infected patients with acute HCV infection, three patients with very high viral load at baseline relapsed after 6 weeks of ledipasvir plus sofosbuvir therapy.[14] The strength and specificity of HCV-specific T-cell responses during acute hepatitis C might be weaker in HIV-positive individuals, a finding that is independent from detectable HIV viraemia.[27] Thus, the relevance of high baseline viral load in patients with acute hepatitis C might differ between patients with monoinfection and individuals with HIV co-infection. More data are required to answer the question of whether treatment with ledipasvir plus sofosbuvir can be safely shortened to 6 weeks in all patients with acute hepatitis C presenting with a baseline viral load of more than 10 000 000 IU/mL.

Short-course treatment of acute hepatitis C with ledipasvir plus sofosbuvir was effective even in patients with other negative predictive baseline factors associated with chronicity or treatment failure; an unfavourable *IFNL3* (*IFNL4*) genotype (type CT or TT) was present in eight patients, and most patients were men (60%), had a BMI of more than 25 kg/m² (60%), and were older than 40 years (70%).

Our findings show a remarkably rapid improvement of biochemical disease measures during treatment with ledipasvir plus sofosbuvir. Most patients had very high concentrations of liver enzymes at screening or baseline,

including seven patients with alanine aminotransferase concentrations of more than 1000 IU/mL. After only 4 weeks, alanine aminotransferase and serum bilirubin concentrations had reduced to within the normal range in 17 of the 20 patients. Acute HCV infection is associated with a widely altered inflammatory milieu,[28] indicating a profound activation of the host's immune response. Our findings suggest that stopping viral replication by direct-acting antiviral therapies immediately interrupts detrimental immune responses. Thus, our results would support immediate treatment of acute hepatitis C in patients with pre-existing liver diseases who are at particular risk of prolonged HCV-associated severe inflammation. Moreover, acute hepatitis C is a disease that can cause symptoms for several weeks or months even in otherwise healthy individuals. Our results suggest that the duration of liver disease can be substantially shorted by early antiviral therapy.

Some patients treated in this trial might have had clearance of HCV infection even without antiviral treatment. Symptomatic acute hepatitis C is associated with a higher chance of HCV clearance and thus the high frequency of symptoms and jaundice in this cohort might have contributed to the high proportion of patients with sustained virological response. Spontaneous clearance of acute hepatitis C was reported in 21% of patients in our previous randomised Hep-Net Acute HCV-III study,[3] which applied similar inclusion criteria to the present study. Indeed, one patient who had high HCV RNA viral load at screening and therefore started treatment with ledipasvir plus sofosbuvir was later identified as having had a viral load of less than 15 IU/mL at baseline. However, viral loads can fluctuate in patients with acute hepatitis C and spontaneous relapses occurred during observation in up to 50% of patients in our previous trial.[3] The mean time between first diagnosis of acute hepatitis C and start of antiviral therapy in our present study was 32·8 days. Thus, the frequently recommended "wait for 4–6 weeks" strategy in acute hepatitis C was actually followed for most patients in this study. Moreover, one advantage of early versus delayed antiviral therapy is that fewer patients are lost to follow-up. One important finding of our previous randomised trial comparing immediate treatment with an approach of 12 weeks of observation was that 42% of patients were lost to follow-up or dropped out when assigned to delayed therapy compared with 25% assigned to immediate treatment.[3]

Obvious limitations of this pilot trial need to be considered. Since acute hepatitis C is a rare disorder leading to a recruitment time of more than 1 year in this nationwide study, only a small number of patients with acute hepatitis C were studied. Therefore, the findings need to be confirmed in larger trials and registries. Patients included in this trial were well selected according to inclusion and exclusion criteria and adherent to the study protocol. By contrast, in a real-world setting most patients with acute hepatitis C in high-income countries are individuals who inject drugs, who might be less adherent to treatment in distinct settings than are the general population.[29] An under-reporting of injecting risk behaviours is always possible and the proportion of patients who acquired the infection by sexual transmission might have been lower. We also do not know the outcome of the six patients who were ineligible at screening. We believe that once-daily treatment with ledipasvir plus sofosbuvir should be feasible for people who inject drugs. Only patients with HCV genotype 1 infection were included in the study; therefore, whether acute HCV genotype 2–6 infections can also be cured with 6 weeks of therapy is still unclear. Furthermore, the optimum treatment duration of acute hepatitis C has not yet been established. It might be possible that even 4 weeks of therapy could be sufficient for some patients with acute hepatitis C, as suggested by a recent preliminary report.[16] Moreover, the effects of other direct-acting antiviral combinations need to be investigated because plasma half-lives of currently investigated or approved NS5A inhibitors differ substantially.

What could be the future role of early treatment of acute hepatitis C when current treatment of chronic hepatitis C is effective in more than 95% of patients? In the absence of a vaccine against HCV, early treatment of acute hepatitis C is likely to be needed to prevent the spread of HCV in high-risk populations. HCV eradication strategies should therefore not only include wide access to treatment of chronic hepatitis C but also include efforts to allow immediate therapy of individuals who could transmit the virus to other individuals.[30] Early treatment of acute hepatitis C will also shorten disease duration and reduce infection-associated morbidity. Medical health professionals infected after occupational exposure would also benefit from treatment of acute hepatitis C because they could continue to work. Finally, early shorter treatment of acute hepatitis C could potentially be cost saving compared with the 8–12 weeks needed for the treatment of chronic hepatitis C. Additionally, shorter observation times and lower costs for repeated diagnostics represent additional advantages of treatment of acute hepatitis C.

In conclusion, treatment for 6 weeks with ledipasvir plus sofosbuvir was well tolerated and highly effective in patients with acute HCV genotype 1 monoinfection. Short-duration treatment of acute hepatitis C could be cost saving compared with treatment of chronic hepatitis C and could prevent the spread of HCV in high-risk populations. Antiviral treatment with an interferon-free regimen rapidly improves symptoms of acute hepatitis.

Contributors

KD, HW, MC, DvW, AK, MPM, and SH planned and designed the study and wrote the protocol. KD, CDS, ES, TMW, GG, HK, US, JW, JSzW, APat, MC, AU, CZ, SZ, MPM, and HW were responsible for patient recruitment and treated patients in the trial. KW and AK were the central trial biostaticicans. Central trial management was done by DvW and central trial physicians were KD and HW. APap and HvdL participated in study monitoring and study management. KD, AK, KW, and HW participated in data analysis and writing of the report. All authors read and approved the final version of the report.

Declaration of interests
KD has received lecture fees from Gilead, AbbVie, and MSD. ES has received personal fees from Gilead, BMS, MSD/Merck, AbbVie, and Janssen. TMW has received lecture fees/consulting fees from AbbVie, BMS, Gilead, Novartis, and Janssen. HK has received research funding from AbbVie, Arrowhead, BMS, Gilead, Janssen, MSD, and Novartis, and has served as a speaker and/or an advisory board member for AbbVie, BMS, Gilead, Hexal, Janssen, and MSD. JSzW has received personal fees from Gilead and AbbVie. MC has served as a speaker and/or an advisory board member for AbbVie, BMS, Boehringer Ingelheim, Biogen Idec, Falk, Gilead, Janssen, MSD/Merck, Roche Diagnostics, Roche Pharma, and Siemens. AU reports grants and personal fees from Gilead. CZ has received travel grants from BMS, Gilead, and Janssen. SZ has received consultancy fees and is a member of the speakers' bureau for AbbVie, BMS, Gilead, Janssen, and MSD/Merck, and reports a grant from Gilead. MPM reports grants and personal fees from Roche, BMS, Gilead, Boehringer Ingelheim, Novartis, MSD/Merck, Janssen, GlaxoSmithKline, Biotest, Achillion, and AbbVie. HW reports grants from AbbVie, Gilead, Roche, Roche Diagnostics, Abbott, Myr GmbH, and Eiger, and reports consulting fees or honoraria from BMS, AbbVie, Abbott, Gilead, Novartis, Roche, MSD/Merck, Janssen, Transgene, Roche Diagnostics, Boehringer Ingelheim, and Eiger. HW is a board member for AbbVie, Abbott, BMS, Boehringer Ingelheim, Gilead, Eiger, Roche, Novartis, and Myr GmbH; has received consultancy fees from Siemens, Eiger, and Janssen; and has received personal fees from OmniaMed and Falk. All other authors declare no competing interests.

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