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「研究成果の刊行物・別刷」

Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial

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Summary

Background Compared with other countries, patients with chronic hepatitis C infection in Japan tend to be older, have more advanced liver disease, and are more likely to have been previously treated for hepatitis C. We aimed to assess the efficacy and safety of an all-oral, fixed-dose combination of the hepatitis C virus NS5A inhibitor ledipasvir and the NS5B nucleotide polymerase inhibitor sofosbuvir with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with chronic genotype 1 hepatitis C virus infection.

Methods In this randomised, open-label study, we enrolled patients from 19 clinical Japanese centres. Patients were randomly assigned (1:1) to receive either ledipasvir (90 mg) and sofosbuvir (400 mg) or ledipasvir, sofosbuvir, and ribavirin (dosed according to the Japanese Copegus product label—ie, patients ≤60 kg received 600 mg daily, patients >60 kg to ≤80 kg received 800 mg daily, and patients >80 kg received 1000 mg daily) orally once daily for 12 weeks. After completion or early discontinuation of treatment, patients were followed up off-treatment for 24 weeks. Eligible patients were at least 20 years of age with chronic genotype 1 hepatitis C virus infection with serum hepatitis C virus RNA concentrations of at least 5 $\log_{10}$ IU/mL, creatinine clearance of at least 1·0 mL/s, and a platelet count of at least 50×10^9 per L. An interactive web response system was used to manage patient randomisation and treatment assignment. Randomisation was stratified by the presence or absence of cirrhosis for treatment-naive patients and stratified by presence or absence of cirrhosis and by previous treatment category (relapser or breakthrough, non-responder, or interferon-intolerant) for previously treated patients. Within each strata, patients were sequentially assigned to either treatment with ledipasvir-sofosbuvir or ledipasvir-sofosbuvir plus ribavirin in a 1:1 ratio with block size of 4. The primary endpoint was sustained virological response 12 weeks after completion of treatment (SVR12) assessed in all patients who were randomly assigned and received at least one dose of study drug; safety outcomes were assessed in all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01975675.

Findings Between Oct 15, 2013 and Dec 13, 2013, 341 patients were randomly assigned to treatment groups and received at least one dose of study treatment. SVR12 was achieved in all 171 (100%) patients (83 of 83 treatment naive and 88 of 88 treatment experienced) receiving ledipasvir-sofosbuvir (95% CI 98–100) and 167 (98%) of 170 patients (80 of 83 treatment naive and 87 of 87 treatment experienced) receiving ledipasvir-sofosbuvir plus ribavirin (95% CI 95–100). Of the 76 patients with baseline NS5A resistant variants, 75 (99%) achieved SVR12. Two (1·2%) of 170 patients in the ledipasvir-sofosbuvir plus ribavirin group discontinued treatment because of adverse events. The most common adverse events were nasopharyngitis (50 [29·2%] of 171), headache (12 [7·0%] of 171), and malaise (nine [5·3%] of 171) in patients receiving ledipasvir-sofosbuvir; and nasopharyngitis (40 [23·5%] of 170), anaemia (23 [13·5%] of 170), and headache in those receiving ledipasvir-sofosbuvir and ribavirin (15 [8·8%] of 170).

Interpretation Although existing regimens for the treatment of hepatitis C virus are effective for many patients, medical needs remain unmet, particularly in Japan where the population with hepatitis C virus genotype 1 is generally older and treatment-experienced, with advanced liver disease. The efficacy, tolerability, and absence of drug–drug interactions of ledipasvir-sofosbuvir suggest that it could be an important option for treatment of genotype 1 hepatitis C virus in Japanese patients.

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Introduction

The prevalence of chronic hepatitis C virus infection in Japan is estimated at up to 2 million people (1·6–2% of the population).[1] Of these, roughly 70% have genotype 1 hepatitis C virus, the most common hepatitis C virus strain worldwide and the most difficult to cure with

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Research in context

Evidence before this study

In January, 2013, we consulted Japanese hepatitis C virus experts and did a multi-institution survey to confirm the demographic and disease characteristics of patients with chronic hepatitis C virus in Japan. Data from this survey suggested that most Japanese patients with hepatitis C virus are elderly (65–76% are >60 years old), more than half are treatment-experienced, and nearly 30% have advanced fibrosis. Fewer than 10% of patients were willing or able to receive interferon. Furthermore, we consulted comprehensive reviews of hepatitis C virus and its treatment in Japan and hepatitis C virus treatment guidelines issued by the Japan Society of Hepatology. Finally, we did PubMed searches for Articles using the terms "HCV treatment" and "Japan" on June 3, 2013 and Nov 25, 2014. There were no language restrictions for this search.

In Japanese patients, telaprevir for 12 weeks with peginterferon and ribavirin for 24 weeks resulted in a sustained virological response rate of 80–87% in treatment-naive patients, 85–88% in previous relapsers, and 75–100% in previous non-responders. In the CONCERTO-4 study, treatment with simeprevir plus peginterferon and ribavirin for 24 weeks led to sustained virological response in 92% of treatment-naive patients, 100% of previous relapsers, and 39% of previous non-responders. In a phase 2 study, a sustained virological response rate of 95–100% was reported in treatment-experienced Japanese patients who received vaniprevir (100 mg, 300 mg, or 600 mg) for 4 weeks with peginterferon plus ribavirin for 6–72 weeks. Safety and tolerability of these regimens is limited by the need for concomitant interferon and ribavirin combined with adverse events and laboratory abnormalities associated with the hepatitis C virus NS3/4A protease inhibitor.

Recently, the all-oral, 24-week regimen of daclatasvir (NS5A inhibitor) plus asunaprevir (NS3A protease inhibitor) was approved in Japan for specific populations. In a phase 3 trial, SVR12 was achieved by 88% of treatment-naive, interferon-ineligible patients and 81% of previous non-responders. Importantly, of those who did not achieve sustained virological response, 65% had hepatitis C virus NS5A resistance-associated variants (L31M/V or Y93H) at baseline and 85% had resistance-associated variants to both daclatasvir and asunaprevir at the time of virological failure. Japanese treatment guidelines recommend use of this regimen in a limited population and require assessment of resistance-associated variants before initiating therapy

Added value of this study

In this study, we deliberately included patients who have been under-represented in trials—elderly patients and those who cannot receive interferon—as well as patients with characteristics that have been associated with reduced sustained virological response rates—patients with resistance-associated variants at baseline, cirrhosis, and treatment-experienced patients. Treatment with the single-tablet regimen of ledipasvir and sofosbuvir taken once daily for 12 weeks was well tolerated and cured all patients treated. The absence of drug interactions means that it could be used irrespective of concomitant medical conditions and treatment.

Implications of all the available evidence

Although existing regimens for the treatment of hepatitis C virus are effective for many patients, important medical needs remain unmet, particularly in Japan where the population with hepatitis C virus genotype 1 is generally older and treatment-experienced, with advanced liver disease. The efficacy, tolerability, and absence of drug–drug interactions of ledipasvir-sofosbuvir suggest that it could be an important option for treatment of genotype 1 hepatitis C virus in a broad range of Japanese patients.

interferon-based treatments. Japanese patients with hepatitis C virus are older (65–76% are >60 years), frequently treatment experienced (with interferon-based therapies), and at high risk of developing hepatocellular carcinoma.[1] Guidelines issued by the Japan Society of Hepatology for patients with genotype 1 hepatitis C virus recommend as the first treatment of choice 12 weeks of triple therapy with the hepatitis C virus NS3/4A protease inhibitor simeprevir, pegylated interferon alfa, and ribavirin followed by 12–36 additional weeks of pegylated interferon alfa and ribavirin if the patient is eligible for and tolerant of interferon.[2] Although this combination provides high rates of sustained virological response (defined as hepatitis C virus RNA <lower level of quantification [LLOQ] after completion of antiviral therapy for chronic hepatitis C infection) in treatment-naive patients and patients who have previously relapsed who are eligible to receive interferon, sustained virological response in patients with previous non-response to treatment is substantially reduced (36–53%).[3–5] Moreover, the side-effects and drug interactions associated with protease inhibitor regimens are problematic for patients with progressive liver disease and comorbid conditions, and for patients with relative or absolute contraindications to interferon or ribavirin.[6,7] For patients who cannot receive interferon, a regimen of daclatasvir plus asunaprevir for 24 weeks is recommended.[2] Although this combination provides an alternative interferon-free regimen, this drug combination is only approved for selected patient populations (patients who have Y93 or L31 mutations in the NS5A region of the hepatitis C virus are not recommended to receive this therapy),[2] has suboptimum efficacy and resistance profiles,[8] and is associated with specific toxic effects.[9,10] An unmet medical need for a simple, safe, and effective regimen that can be used in an ageing population with progressive liver disease remains.

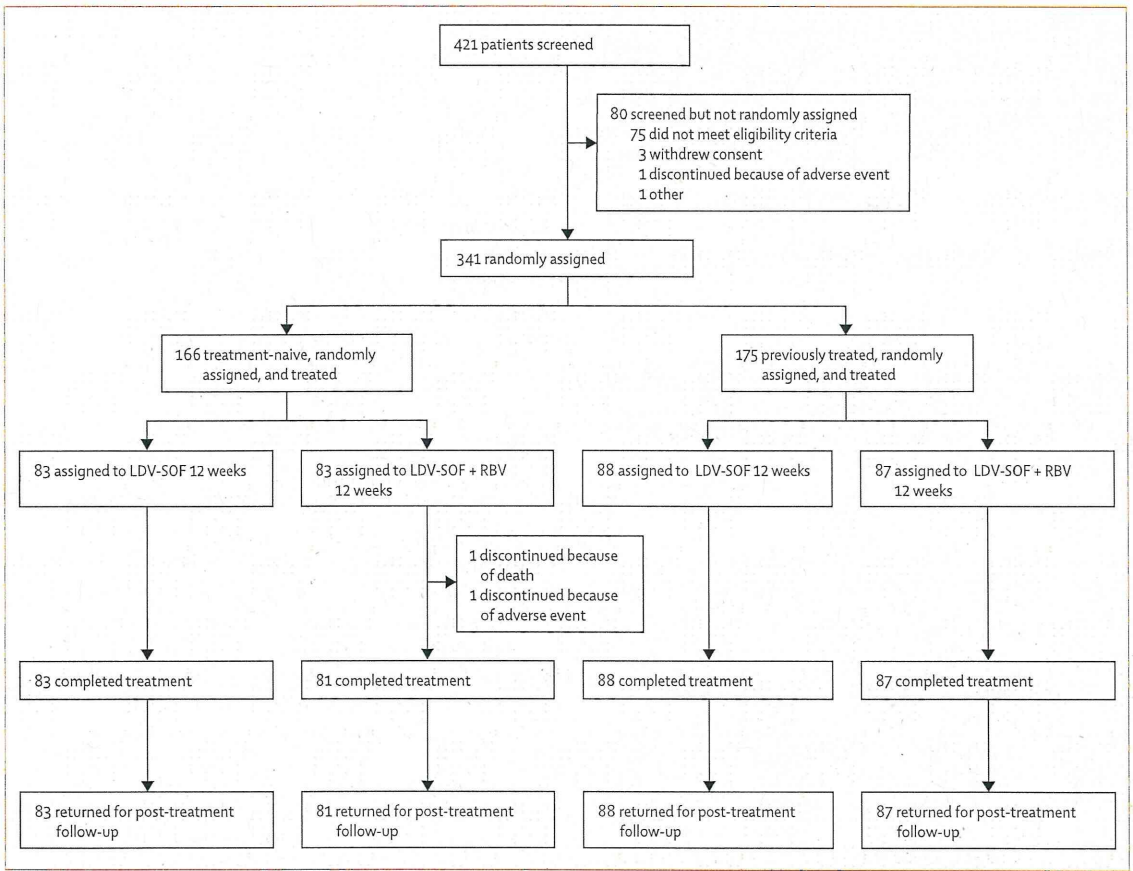

Figure: **Trial profile**
LDV=ledipasvir. SOF=sofosbuvir. RBV=ribavirin.

Sofosbuvir is a nucleotide analogue inhibitor of the hepatitis C virus non-structural protein 5B (NS5B) polymerase that is approved in the USA, Europe, and other countries for the treatment of patients with chronic hepatitis C virus infection.[11] Ledipasvir is a novel hepatitis C virus NS5A inhibitor that has shown potent anti-hepatitis C virus activity.[12] In three phase 3 trials done in the USA and Europe, 12 weeks of treatment with the ledipasvir-sofosbuvir fixed-dose combination was well tolerated and resulted in high rates (94–99%) of sustained virological response in treatment-naive and previously treated patients with genotype 1 hepatitis C virus, including those with cirrhosis.[13–15] Subsequently, ledipasvir-sofosbuvir received marketing authorisation in these regions in 2014.

We did a phase 3 trial to assess the efficacy and safety of 12 weeks of the ledipasvir-sofosbuvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C virus infection. The primary efficacy endpoint of this study was sustained virological response 12 weeks after the end of treatment (SVR12).

Methods

Study design and participants

In this randomised, open-label, phase 3 trial, we enrolled patients with chronic genotype 1 hepatitis C virus infection at 19 clinical sites in Japan. Planned patient enrolment was 150 treatment-naive and 150 treatment-experienced patients (appendix). Eligible patients were at least 20 years of age with chronic genotype 1 hepatitis C virus infection with serum hepatitis C virus RNA concentrations of at least 5 $\log_{10}$ IU/mL and creatinine clearance of at least 1·0 mL/s (Cockcroft-Gault equation). We did not use an upper age limit. Patients with hepatic decompensation (as shown by the presence of ascites, encephalopathy, or a history of variceal haemorrhage), bodyweight less than 40 kg, or coinfection with hepatitis B or HIV were excluded. Consistent with a population with progressive liver disease, no minimum neutrophil count was needed and patients with a platelet count of at least 50×10^9 platelets per L were eligible for participation. Up to 40% of patients enrolled in the study could have had compensated cirrhosis. The presence of cirrhosis was established either by liver biopsy (eg, a Metavir

See Online for appendix