Efficacy and safety of 3-week response-guided triple direct-acting antiviral therapy for chronic hepatitis C infection: a phase 2, open-label, proof-of-concept study

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Summary

Background To shorten the course of direct-acting antiviral agents for chronic hepatitis C virus (HCV) infection, we examined the antiviral efficacy and safety of 3 weeks of response-guided therapy with an NS3 protease inhibitor and dual NS5A inhibitor–NS5B nucleotide analogue.

Methods In this open-label, phase 2a, single centre study, Chinese patients with chronic HCV genotype 1b infection without cirrhosis were randomly allocated by a computer program to one of three treatment groups (sofosbuvir, ledipasvir, and asunaprevir; sofosbuvir, daclatasvir, and simeprevir; or sofosbuvir, daclatasvir, and asunaprevir) until six patients in each group (1:1:1) achieved an ultrarapid virological response (plasma HCV RNA <500 IU/mL by day 2, measured by COBAS TaqMan HCV test, version 2.0). Patients with an ultrarapid virological response received 3 weeks of therapy. Patients who did not achieve an ultrarapid response were switched to sofosbuvir and ledipasvir for either 8 weeks or 12 weeks. The primary endpoint was the proportion of patients with a sustained virological response at 12 weeks (SVR12) after treatment completion, analysed in the intention-to-treat population. All patients who achieved an ultrarapid virological response were included in the safety analysis. This trial is registered with ClinicalTrials.gov, number NCT02470858.

Findings Between April 5, 2015, and April 15, 2015, 26 eligible patients were recruited. 12 patients were assigned to sofosbuvir, ledipasvir, and asunaprevir; six to sofosbuvir, daclatasvir, and simeprevir; and eight to sofosbuvir, daclatasvir, and asunaprevir. Six patients in each group achieved an ultrarapid virological response (18 [69%]). All patients with an ultrarapid virological response who were given 3 weeks of triple therapy achieved SVR12. The most common adverse events were fatigue (one [17%] of six patients receiving sofosbuvir, ledipasvir, and asunaprevir; one [17%] of six patients receiving sofosbuvir, daclatasvir, and simeprevir; and two [33%] of six patients receiving sofosbuvir, daclatasvir, and asunaprevir) and headache (one [17%] patient in each group). No patients experienced any serious adverse events.

Interpretation In this proof-of-concept study, all patients with chronic HCV without cirrhosis who achieved an ultrarapid virological response on triple direct-acting antiviral regimens by day 2 and received 3 weeks of treatment were cured, with excellent tolerability. By shortening the duration of therapy from the currently recommended 12 weeks to 3 weeks, we could drastically reduce the cost of therapy and the rate of adverse events. Further large-scale studies should be done to confirm our findings.

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Introduction

Treatment of hepatitis C virus (HCV) infection has entered a new era with the emergence of direct-acting antiviral agents. By 2015, the US Food and Drug Administration (FDA) and EU had approved three new direct-acting antiviral drugs—sofosbuvir, simeprevir, and daclatasvir—for the treatment of HCV infection as part of combination regimens.[1,2] 91–100%[3–5] of individuals infected with HCV genotype 1 treated with 8–12 weeks of sofosbuvir and ledipasvir once daily, and 98–100%[6] of patients who received 12–24 weeks of sofosbuvir and daclatasvir once daily, achieved sustained virological response at 12 weeks (SVR12). The cost of such regimens is onerous[7] and this has adversely affected treatment access and drug compliance, and has encouraged drug counterfeiting.[8,9] A major challenge is to reduce treatment cost without affecting efficacy by shortening the duration of treatment.[10,11] Attempts to reduce the duration of therapy to 6 weeks through the addition of ribavirin to sofosbuvir and ledipasvir resulted in many patients relapsing after treatment,[12] but the addition of an experimental NS3/4A protease inhibitor (GS-9451) or an experimental non-nucleoside polymerase inhibitor (GS-9669) yielded an SVR12 in 95% of patients.[13]

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Research in context

Evidence before this study

We searched PubMed from Jan 1, 2010, to April 14, 2016, for articles published in English using a combination of the medical subject headings "HCV treatment" and "antiviral agent" as search terms. Two related clinical trials have been reported for hepatitis C virus (HCV) combination therapy studies (phase 2a). These trials have shown promising safety and efficacy using combination direct-acting antiviral drugs.

Added value of this study

Although our study is small, we showed high rates of sustained viral response at 12 weeks with use of the 3-week triple direct-acting antiviral therapy, which supports the possibility that this ultrashort regimen might be effective for some patients infected with HCV.

Implications of all the available evidence

Our study demonstrated that the duration of therapy of pan-oral direct-acting antiviral agents could be drastically shortened from the current recommended 12 weeks to only 3 weeks with triple direct-acting antiviral therapy, containing NS5B, NS3, and NS5A inhibitors, in non-cirrhotic Chinese patients infected with chronic HCV genotype 1b and who had an ultrarapid virological response. This could have great therapeutic, public health, and economic implications because genotype 1b rather than 1a is the predominant strain in Asian populations (estimated at about 50 million). Further large-scale studies with the use of a response-guided approach are needed in other populations with different genotypes and in cirrhotic patients.

Mathematical modelling of HCV RNA changes during therapy suggests that a more rapid second-phase viral decline should allow for a shorter treatment duration.[14] Nucleoside analogue inhibitors do not generate fast second-phase declines such as those with HCV protease inhibitors.[14–17] Thus, we postulated that addition of an approved protease inhibitor, such as simeprevir or asunaprevir to sofosbuvir and ledipasvir or daclatasvir might induce a more rapid second-phase HCV RNA decline, allowing for a shorter treatment duration.

Therefore, we did a proof-of-concept, response-guided therapy clinical study to investigate the efficacy and the safety of 3 weeks of triple direct-acting antiviral therapy, containing NS5B, NS3, and NS5A inhibitors, in Chinese patients with chronic HCV genotype 1b infection without cirrhosis who achieved an ultrarapid initial viral response (uRVR), defined by a serum HCV RNA lower than 500 IU/mL within the first 2 days of dosing. We focused on patients infected with genotype 1b because this is the predominant strain in Asian populations (estimated at about 50 million), although this genotype can also be found in other populations.[18,19]

See Online for appendix

Methods

Study design and participants

This was an open-label, proof-of-concept, phase 2a study done at a single centre (Humanity and Health Medical Centre, Hong Kong SAR, China). Participants were identified using the Beijing 302 Hospital of PLA–Hong Kong Humanity and Health Medical Group, Hepatitis C Diagnosis and Treatment Centre database, which had records for 503 patients infected with HCV by the time of the study. People who satisfied all the inclusion and exclusion criteria and who consented were consecutively enrolled. Key inclusion criteria were: older than 18 years; documented chronic HCV genotype 1b infection for more than 6 months; a baseline plasma HCV RNA concentration of 10^4–10^7 IU/mL; and absence of cirrhosis as assessed by liver biopsy or by liver stiffness measurement less than 12·5 kPa. Key exclusion criteria were: hepatitis B virus (HBV) or HIV infection; chronic liver disease of a non-HCV aetiology; hepatocellular carcinoma or other malignancy; drug or alcohol misuse; pregnant or nursing woman; known hypersensitivity to pharmaceutical products used in this study; and any other medical disorders or clinical conditions (eg, substantial cardiopulmonary, neurological, renal, haematological, autoimmune disorders, and any malignancy) that could interfere with the study. Treatment-experienced patients had been exposed to interferon-based therapy previously.

Written informed consent was obtained from all patients. The study was approved by the independent ethics committee at the study centre and was done in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. An independent data and safety monitoring committee reviewed the progress of the study. The full protocol is included in the appendix.

Randomisation and masking

All eligible patients were randomly allocated by a computerised system to one of three treatment groups (sofosbuvir, ledipasvir, and asunaprevir; sofosbuvir, daclatasvir, and simeprevir; or sofosbuvir, daclatasvir, and asunaprevir) until six patients achieved a uRVR in each group. The computer sequence was generated by a biostatistician (JC) who assigned them to trial groups but was not involved in the rest of the trial.

The trial was open label; patients and investigators were aware of group assignment.

Procedures

Patients received sofosbuvir, ledipasvir, and asunaprevir; sofosbuvir, daclatasvir, and simeprevir; or sofosbuvir, daclatasvir, and asunaprevir. Doses were as follows: sofosbuvir 400 mg once daily; ledipasvir 90 mg once daily; daclatasvir 60 mg once daily; simeprevir 150 mg