Variable short duration treatment versus standard treatment, with and without adjunctive ribavirin, for chronic hepatitis C: the STOP-HCV-1 non-inferiority, factorial RCT

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Declared competing interests of authors: Graham S Cooke has received fees from Merck Sharp & Dohme Corp. (Whitehouse Station, NJ, USA) and Gilead Sciences, Inc. (Foster City, CA, USA), unrelated to this work. In addition, Graham S Cooke is supported, in part, by the Biomedical Research Centre of Imperial College Healthcare NHS Trust (London, UK) and is a National Institute for Health Research (NIHR) research professor. Sarah Pett has received grants from Gilead Sciences, Inc. and ViiV Healthcare Ltd (Research Triangle, NC, USA), unrelated to this work. Richard Gilson reports grants from AbbVie (Chicago, IL, USA) and Gilead Sciences, Inc., unrelated to this work. Sumita Verma reports grants and consultancy fees from Gilead Sciences, Inc., and personal fees from AbbVie, unrelated to this work. Stephen D Ryder has carried out consultancy work for Gilead Sciences, Inc. Stephen T Barclay reports grants and personal fees from AbbVie and Gilead Sciences, Inc., unrelated to this work. Sanjay Bhagani reports personal fees from AbbVie and Gilead Sciences, Inc., and is the spouse of an AbbVie employee. Mark Nelson reports personal fees and grants from Merck Sharp & Dohme Corp., AbbVie, Gilead Sciences, Inc. and Bristol Myers Squibb™ (New York, NY, USA), unrelated to this work. In addition, he has a patent for AbbVie pending. Chin Lye Ch'Ng reports grants and personal fees from AbbVie and Gilead Sciences, Inc., unrelated to this work. Martin Wiselka reports personal fees from Merck Sharp & Dohme Corp., AbbVie and Gilead Sciences, Inc., unrelated to this work. Daniel Forton has received research funding and personal fees from Gilead Sciences, Inc. and personal fees from AbbVie, unrelated to this work. Stuart McPherson reports personal fees from Gilead Sciences, Inc., Merck Sharp & Dohme Corp. and AbbVie, as well as a grant from Gilead Sciences, Inc., unrelated to this work. Ann Sarah Walker is a NIHR Senior Investigator.

Published October 2021
DOI: 10.3310/eme08170

Scientific summary

The STOP-HCV-1 RCT

Efficacy and Mechanism Evaluation 2021; Vol. 8: No. 17
DOI: 10.3310/eme08170

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Scientific summary

Background

The recent and rapid development of oral treatment options for hepatitis C virus (HCV) has encouraged an ambitious strategy to eliminate viral hepatitis as a global public health threat by 2030, with the target of treating 80% of those chronically infected with HCV. Licensed durations of 8–12 weeks' therapy with direct-acting antivirals (DAAs) are significantly shorter, more tolerable and more effective than previous interferon-based therapies, but some patients still find it challenging to complete a full treatment course. Such patients will become an increasingly important part of clinical practice as treatment coverage expands to reach marginalised groups.

Objectives

The primary objectives of the STOP-HCV-1 (Stratified Treatment OPtimisation for HCV-1) trial were to test:

- whether or not a biomarker-stratified short-course HCV first-line treatment [with variable duration of between 4 and 7 weeks determined by patient baseline viral load (VL)] followed by 12 weeks of retreatment for those failing therapy was non-inferior to a fixed-duration 8-week first-line treatment followed by 12 weeks of retreatment for those failing therapy, in terms of overall HCV cure in patients with minimal fibrosis and chronic genotype 1 or 4 HCV infection
- the benefits and risks of adding adjunctive ribavirin to 4–8 weeks' first-line therapy on HCV cure on first-line treatment.

Secondary objectives included testing the impact of biomarker-stratified first-line treatment on cure on first-line treatment (i.e. excluding retreatment responses) and testing whether or not retreatment with 12 weeks of an alternative combination regimen, given after detecting virological failure on first-line treatment, still achieved cure in the majority of the small proportion in whom short-course first-line treatment fails.

Methods

Design

An open-label, multicentre, factorial randomised controlled trial.

Setting

Fourteen NHS trusts, including outpatient infectious disease and hepatology services. Patients were identified through both hepatology and infectious disease services caring for patients with chronic HCV infection in sites linked to NHS Operational Delivery Networks for hepatitis.

Participants

Inclusion criteria

- Aged $\geq$ 18 years.
- Infected with HCV genotype 1a/1b or 4 with access to first-line treatment appropriate for the genotype.

- At least one episode of detectable viraemia in the 6 months prior to randomisation (as determined by quantitative HCV ribonucleic acid, qualitative assay or HCV genotyping), with no intervening undetectable results.
- Plasma HCV VL greater than lower limit of quantification at screening.
- No evidence of significant liver fibrosis resulting from any aetiology.
- Body mass index $\geq$ 18 kg/m^2.
- Laboratory tests: platelets $\geq 60 \times 10^9$/l, haemoglobin > 12 g/dl (male) or > 11 g/dl (female), creatinine clearance (estimated using the Cockcroft–Gault formula) $\geq$ 60 ml/minute and international normalised ratio < 1.5.
- Screening HCV VL < 10,000,000 IU/ml.
- Written informed consent obtained from the patient.

If patients were infected with human immunodeficiency virus (HIV), then an additional eligibility criterion was:

- on antiretrovirals with a HIV VL of < 50 copies/ml for > 24 weeks at the screening visit.

Exclusion criteria

- Previous exposure to DAAs for this infection.
- Lactating, pregnant, planning to become pregnant or not willing to use effective contraception during the study and for 4 months after the last dose of the study medication (female patients only).
- Currently taking ethinyloestradiol-containing medicinal products, such as those contained in most combined oral contraceptives or contraceptive vaginal rings (female patients only).
- Planning pregnancy with female partner or not willing to use effective contraception during the study and for 7 months after the last dose of the study medication (male patients only).
- Malignancy within 5 years prior to screening.
- Any condition that, in the judgement of the investigator, might limit the patient's life expectancy.
- Currently receiving medication known to interact with study medication.
- A disorder that may cause ongoing liver disease, including, but not limited to, active hepatitis B virus and ongoing alcohol misuse.
- Any disorder that, in the opinion of the investigator, may have a significant negative impact on the ability of the patient to adhere to the trial regimen.
- Use of other investigational products within 60 days of screening.
- Known hypersensitivity to any active ingredient and/or excipients of the study medicines.
- History of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous 6 months.
- Haemoglobinopathies.

Interventions

Eligible participants were randomised to fixed-duration therapy (of 8 weeks) or variable-duration (continuous-scale) ultrashort therapy [variable ultrashort strategy (VUS)], initially for 4–6 weeks stratified by screening VL (VUS1, mean 32 days of treatment), and, subsequently, for 4–7 weeks (VUS2, mean 39 days of treatment), predominantly with ombitasvir, paritaprevir, ritonavir (Viekirax®; AbbVie, Chicago, IL, USA), and dasabuvir (Exviera®; AbbVie, Chicago, IL, USA) or ritonavir. All patients in whom first-line treatment was unsuccessful were immediately retreated with 12 weeks' sofosbuvir, ledipasvir (Harvoni®; Gilead Sciences, Inc., Foster City, CA, USA) and ribavirin.

Follow-up

All participants were followed up on days 3, 7, 14 and 28 (post randomisation), at the end of therapy (EOT), then 4-weekly until 12 weeks post EOT and then, finally, at 24 weeks post EOT.

Sample size

Assuming a 98% cure rate overall for the control group, for a 4% non-inferiority margin, 80% power, a one-sided test and an alpha of 0.025, the required sample size for the biomarker-stratified duration comparison was 408 patients, allowing for 5% early withdrawal. A total of 306 patients randomised to adjunctive ribavirin (or not) provided 75–85% power to identify a 10% improvement in first-line cure for first-line cure rates of 83–86% without ribavirin and 93–96% with ribavirin (two-sided $\alpha = 0.05$), allowing for 5% early withdrawal as above.

Results

Baseline characteristics

Sixty-two (31%) participants were female, with a median age of 45 [interquartile range (IQR) 37–53] years. Median enrolment VL was 741,946 (IQR 249,097–1,872,136) IU/ml. A total of 166 (82%) patients were infected with genotype 1a, 34 (17%) were infected with genotype 1b and two (1%) were infected with genotype 4. All but four (2%) participants received ombitasvir/paritaprevir/ritonavir plus dasabuvir as their first-line treatment. Twenty-seven patients (14%) had a resistance-associated substitution (RAS) to at least one prescribed first-line drug and 68 (34%) were co-infected with HIV. Baseline characteristics were reasonably balanced between randomisation groups.

Follow-up

Thirteen (6%) participants became lost to follow-up (11 on first-line treatment and two on retreatment) and one participant withdrew consent; however, the primary outcome in most cases could be ascertained from routine local measurements of VLs carried out outside the trial. Most visits were attended, with, at most, 4% of visits missed at each first-line visit and, at most, 6% of visits missed at each retreatment visit, other than at EOT plus 8 weeks, when 16% of visits were missed. Nine (5%) participants stopped at least part of their first-line treatment early and 55 (28%) participants reported missing at least one first-line dose. Seven (11%) participants stopped at least part of their retreatment early and 24 (39%) participants reported missing at least one retreatment dose.

Primary end point

All participants achieved a sustained virological response (virus persistently undetectable) 12 weeks after end of therapy (SVR12) after first-line treatment and any retreatment (197/197), a difference of 0% between VUS and fixed-duration strategies [95% confidence interval (CI) −3.8% to 3.7%], within the prespecified 4% non-inferiority margin. There was no evidence of differences in the proportion of patients achieving SVR12 after first-line treatment between those randomised to ribavirin [68% (69/98), 95% CI 67% to 76%] and those not randomised to ribavirin [72% (70/101), 95% CI 65% to 78%] ($p = 0.48$). Among participants allocated to the variable-duration strategy, the proportion achieving SVR12 was 52% in the group treated with ribavirin (25/48, 95% CI 37% to 67%), compared with 44% in the group not treated with ribavirin (22/50, 95% CI 30% to 59%).

Secondary end points

The proportion of participants achieving SVR12 following first-line treatment was significantly lower among those randomised to the variable-duration strategy [48% (47/98), 95% CI 39% to 57%] than among those randomised to the fixed-duration strategy [91% (92/101), 95% CI 86% to 97%] (risk difference −43%, 95% CI −54% to −32%; $p < 0.001$). However, first-line SVR12 was significantly higher in the VUS2 group [72% (23/32), 95% CI 56% to 87%] than in the VUS1 group [36% (24/66), 95% CI 25% to 48%]. Similarly, all participants achieved a sustained virological response (persistently undetectable virus) 24 weeks after the end of therapy (SVR24) after first-line treatment and any retreatment (194/194, risk difference 0%, 95% CI −3.8% to 3.7%), but the rate of first-line SVR24 was significantly lower among participants randomised to variable-duration treatment (risk difference −42%, 95% CI −53% to 31%; $p < 0.001$). There was no evidence of differences in first-line SVR24 by ribavirin randomisation (risk difference 1%, 95% CI −9% to 11%; $p = 0.83$). Participants randomised to

variable-duration treatment were significantly more likely than those randomised to fixed-duration treatment to have both HCV VL rebound and primary first-line treatment failure ($p < 0.001$ and $p = 0.008$, respectively), whereas there was no evidence of difference between those randomised to ribavirin and those not ($p = 0.59$ and $p = 83$, respectively). Twenty-one per cent (41/197) of participants overall had detectable VL 4 weeks after randomisation, with no evidence of differences in the percentages with detectable VL post randomisation between either randomisation ($p > 0.08$). Twenty-five per cent (14/56) of participants developed a new RAS to first-line drugs. Although there was no evidence of differences in the percentages developing RASs between those randomised to variable-duration treatment and those randomised to fixed-duration treatment ($p = 0.77$), those randomised to ribavirin were significantly less likely to develop a RAS [12% (3/26), 95% CI 2% to 30%] than those who were not [38% (11/29), 95% CI 21% to 58%] (risk difference −26%, 95% CI −48 to −6%; $p = 0.01$).

Safety

Ten serious adverse events (SAEs) occurred during the trial, but none was related to study treatment. Five SAEs occurred in each of the variable-duration and fixed-duration groups ($p = 0.69$) and five SAEs occurred in each of the ribavirin and no-ribavirin groups ($p = 0.59$). There were 21 grade 3 or 4 adverse events (AEs), of which 12 were related to the study drug. Sixteen events in nine participants occurred in the variable-duration group and five events in five participants occurred in the fixed-duration group ($p = 0.28$). Fifteen events in nine participants occurred in the ribavirin group and six events in five participants occurred in the no-ribavirin group ($p = 0.28$). Sixteen AEs that led to a change in the study drug (14 in the variable-duration group and two in the fixed-duration group; 12 in the ribavirin group and four in the no-ribavirin group). There were three grade 3 or 4 anaemias (all in the variable-duration ribavirin group).

Conclusions

Unsuccessful first-line short-course therapy did not compromise retreatment with sofosbuvir, ledipasvir and ribavirin (100% SVR12). SVR12 rates were significantly increased when ultrashort treatment varied between 4 and 7 weeks, rather than between 4 and 6 weeks. We found no evidence that ribavirin significantly improved first-line SVR12, but it significantly reduced resistance emergence in those failing first-line treatment.

Trial registration

This trial is registered as ISRCTN37915093, EudraCT 2015-005004-28 and CTA 19174/0370/001-0001

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 17. See the NIHR Journals Library website for further project information.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

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Editorial contact: journals.library@nihr.ac.uk

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The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This report

The research reported in this issue of the journal was funded by the EME programme as project number 14/02/17. The contractual start date was in February 2016. The final report began editorial review in February 2020 and was accepted for publication in June 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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