



Canadian Agency for
Drugs and Technologies
in Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL

TITLE: Triple Therapy for Hepatitis C in Previous Non-responders: A Review of the Clinical Effectiveness and Safety

DATE: 8 December 2014

CONTEXT AND POLICY ISSUES

Hepatitis C virus (HCV) infection affects over 150 million people in the world, and a majority of them will develop chronic infection such as cirrhosis or hepatocellular carcinoma,^{1,2} with death-related direct medical cost projections exceeding US\$6.7 billion between 2010 and 2019 in the US.³ HCV infection is classified into seven major genotypes and multiple subtypes, based on genetic material of different virus strands, with genotype 1 HCV being the most common in North America, and the most resistant to treatment.⁴

Successful treatment of HCV infection is reflected by a sustained virologic response (SVR), which is the absence of detectable levels of viral genetic material in the blood 24 weeks after completion of therapy. The current standard treatment for chronic HCV infection has been a combination of peginterferon- α and ribavirin (PR) for 24 to 48 weeks, which, acting on non-specific pathways, has suboptimal SVR and significant toxicity in treated patients.^{5,6} Recently, new drugs that act on specific targets in the viral life cycle have been developed to directly inhibit viral production.^{7,8} These drugs, referred as direct-acting antiviral medications (DAA), and included protease inhibitors such as boceprevir and telaprevir, can be used alone, together with another DAA, or combined with PR.⁹ Boceprevir and telaprevir, approved by Health Canada in 2011, have demonstrated high cure rates when used together with PR, but adverse event rates and low spectrum activity (genotype 1) have been barriers to their use.^{10,11} In order to improve the pharmacokinetics and tolerability of DAA, a second generation of protease inhibitors such as simeprevir and sofosbuvir have been recently developed and approved for use in Canada in 2013 and 2014, respectively.¹²⁻¹⁵ Simeprevir and sofosbuvir can be used as first-line therapy for the treatment of HCV infection, or because of the high costs associated with the new DAA, in patients who had not responded to standard treatment or first generation DAA.¹⁶⁻²⁵ A recent Therapeutic Review report by CADTH recommended simeprevir for treatment-naïve or -experienced patients with genotype 1 HCV, but could not make a recommendation for sofosbuvir due to a lack of evidence.²⁶

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This Rapid Response report aims to review the clinical effectiveness and safety of simeprevir and/or sofosbuvir combined with PR in patients with chronic hepatitis C genotype 1, 2, 3 or 4 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of simeprevir and/or sofosbuvir combined with peginterferon + ribavirin (PR) in patients with chronic hepatitis C genotype 1 who have had an inadequate response to prior direct acting antiviral (DAA) plus (PR) therapy or prior treatment with PR alone?
2. What is the clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 2 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone?
3. What is the clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 3 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone?
4. What is the clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 4 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone?

KEY FINDINGS

In general, findings from the included studies were consistent on the superiority of simeprevir once daily plus PR therapy to placebo plus PR therapy in terms of SVR in patients with chronic hepatitis C genotype 1 who have had an inadequate response to prior PR therapy. The addition of simeprevir to PR was well tolerated generally, with comparable adverse events rates compared to PR alone. The literature search did not identify evidence on sofosbuvir. There was a lack of evidence on patients with HCV genotypes 2, 3 or 4.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and November 7, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of any relevant titles or abstracts were

retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Population	Adult Patients with chronic hepatitis C genotype 1, 2, 3, or 4 infection who have an inadequate response to direct acting antiviral + PR therapy or PR treatment alone
Intervention	Simeprevir and/or sofosbuvir combined with PR
Comparator	Dual therapy (PR), other triple therapy options
Outcomes	Sustained virological response (SVR), treatment completion, histological changes, relapse, quality of life, liver failure, hepatocellular carcinoma, liver transplants, and mortality (all-cause and liver related). Serious adverse events, adverse events, withdrawals due to adverse events, rash, fatigue, anemia, pruritis, anorectal discomfort, neutropenia, depression, suicidal ideation, and flu-like symptoms
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), and non RCTs.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2009, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included trials was assessed using the Downs and Black²⁷ checklist. Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 307 citations. After screening of abstracts from the literature search and from other sources, 14 potentially relevant studies were selected for full-text review. Three studies met the inclusion criteria and were included in this review.

The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included studies characteristics is provided in Appendix 2.

Study design

Three relevant trials were identified.²⁸⁻³⁰ One trial was a phase IIa placebo-controlled, randomized study, with a treatment time of 28 days, and outcomes measured at the end of 28 days of treatment.²⁸ One trial was a phase IIb double-blind, placebo-controlled, randomized study, with 48 weeks of treatment, and outcomes measured at 24 weeks after the end of treatment.²⁹ One trial was a phase III double-blind, placebo-controlled, randomized study, with 48 weeks of treatment, and outcomes measured at 12 weeks after the end of treatment.³⁰

Population

One trial included 74 treatment-naïve and 37 treatment-experienced patients (non-responders or prior relapsers to PR treatment).²⁸ One trial included 462 treatment-experienced patients (non-responders or relapsers to prior PR treatment).²⁹ One trial included 393 relapsers after prior PR therapy.³⁰

Interventions and comparators

One trial used simeprevir 75, 150, or 200mg once a day plus PR for 28 days.²⁸ One trial used simeprevir 100, or 150mg once a day for 12, 24, or 48 weeks, plus PR for 48 weeks.²⁹ One trial used simeprevir 150 mg once a day plus PR for 12 weeks, then PR alone for 12 or 36 weeks, based on response-guided therapy criteria.³⁰ All trials compared outcomes with similar regimens of placebo plus PR.

Outcomes

One trial measured decline in HCV RNA,²⁸ and two trials measured SVR.^{29,30} All three trials also measured adverse events rates, and treatment discontinuation rates.

Summary of Critical Appraisal

All three trials were randomized, with hypotheses, main outcomes, patient characteristics, finding, and loss to follow-up clearly described.²⁸⁻³⁰ Two studies^{28,29} had a clear and detailed description of the randomization procedure, while one³⁰ described randomization as “centralized” without additional detail. One trial was a phase IIa trial; patients were not blinded to treatment, and it did not report estimates of random variability and actual probability values.²⁸ Two trials reported that power calculations were conducted but it was unclear whether study power was sufficient to detect clinically important effects, as the results of the calculation were not reported.^{28,29} The third study²⁴ reported a power calculation and met the required sample size to detect clinically important effects. All studies outcomes were assessed based on an intention-to-treat population. The findings from the studies can be generalized to the general population under study.

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4.

1. What is the clinical effectiveness and safety of simeprevir and/or sofosbuvir combined with peginterferon + ribavirin (PR) in patients with chronic hepatitis C genotype 1 who have had an inadequate response to prior direct acting antiviral (DAA) plus (PR) therapy or prior treatment with PR alone?

Three trials looked at the clinical effectiveness and safety of simeprevir combined with PR in patients with chronic hepatitis C genotype 1 who have had an inadequate response to prior direct acting antiviral PR therapy.²⁸⁻³⁰ In general, simeprevir plus PR was significantly superior to placebo plus PR in terms of SVR, and was generally well tolerated. The literature search did not identify any study on the effectiveness or safety of sofosbuvir combined with peginterferon + ribavirin (PR) in patients with chronic hepatitis C genotype 1 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone.

A phase IIa RCT in 2011²⁸ evaluated simeprevir efficacy and safety in 74 HVC genotype-1 treatment-naïve and 37 treatment-experienced patients (HCV RNA levels > 10,000 IU/ml), including non-responders and prior relapsers to PR therapy. Treatment-experienced patients received simeprevir 75mg (n = 9), 150mg (n = 9) or 200mg (n = 10) once a day + PR, or placebo once daily + PR (n = 9) for 28 days. Outcomes measured at the end of 28 days of treatment were decline in HCV RNA (please note that due to short follow up time, SRV by definition could not be evaluated in this trial), adverse events rate and treatment discontinuation rate.

The majority of patients (18/28) treated with simeprevir + PR (9/9 prior relapsers and 9/19 non-responders) had HCV RNA < 25 IU/ml at day 28. No patients (0/9) treated with placebo + PR had HCV RNA < 25 IU/ml at day 28. Patients on 150 or 200 mg doses had better HCV RNA decline than those on the 75 mg dose. Similar results were found between 150 and 200 mg doses.

Adverse events were similar in all groups (89.9% of patients on placebo + PR, 89.9% of patients on simeprevir 75 mg/day + PR, 100% of patients on simeprevir 150 mg + PR, and 100% in patients on simeprevir 200 mg + PR). Most adverse events were grade 1 or 2 (mild or moderate), with headache and fatigue being the most common. No treatment discontinuation was found in any group.

A phase IIb, double-blind RCT in 2014²⁹ evaluated the efficacy and safety of simeprevir in 462 HVC genotype-1 treatment-experienced patients (HCV RNA levels > 10,000 IU/ml), including non-responders and prior relapsers to PR therapy. Patients received simeprevir 100 or 150 mg once a day for 12, 24, or 48 weeks + PR, or placebo + PR for 48 weeks. Outcomes were measured at 24 weeks after the end of treatment and included SVR, adverse event rate and treatment discontinuation rate.

SVR rates across different dosages and treatment periods at 24 weeks after completion of treatment were significantly higher in groups on simeprevir + PR than those on placebo + PR (61% to 80% vs 23%; $P < 0.001$). Subgroup analyses showed that SVR rates in simeprevir groups at 24 weeks after end of treatment in patients with null response to prior PR therapy

were 37.5% to 58.8% (18.8% in placebo group), 47.8% to 86.4% in patients with partial prior PR response (8.7% in placebo group), and 76.9% to 88.9% in relapsers (37.0% in placebo group) (*P* value not reported for subgroup analyses)

All groups had similar adverse event rates (rates of any adverse event not reported). Most adverse events were grade 1 or 2, with fatigue and headache being the most common. Permanent discontinuation due to adverse events occurred in 8.8% of simeprevir-treated patients and in 4.5% in placebo-treated patients.

A phase III double-blind RCT in 2014³⁰ evaluated the efficacy and safety of simeprevir in 393 HVC genotype-1 treatment-experienced patients (HCV RNA levels > 10,000 IU/ml), who relapsed after prior PR therapy. Patients received simeprevir 150 mg once a day + PR for 12 weeks, then PR alone for 12 or 36 weeks, based on response-guided therapy criteria, or placebo + PR for 12 weeks, then PR alone for 36 weeks. Outcomes were measured at 12 weeks after the end of treatment, and included SVR, on-treatment failure (non-responders), relapse rate, rates of patients on simeprevir + PR who can shorten therapy, adverse events, and treatment discontinuation rates.

SVR rates at 12 weeks after end of treatment were significantly higher in groups on simeprevir + PR than those on placebo + PR (79.2% vs 36.1%; *P* < 0.001). On-treatment failure rates (non-responders) were significantly lower in groups on simeprevir + PR than those on placebo + PR (3.1% vs 27.1%; *P* < 0.001). Relapse rates were significantly lower in groups on simeprevir + PR than those on placebo + PR (18.5% vs 48.4%; *P* < 0.001). Most patients on simeprevir + PR (92.7%) were able to shorten therapy to 24 weeks.

All groups had similar adverse event rates. Most adverse events were grade 1 or 2, with fatigue and headache being the most common. Permanent discontinuation occurred in 0.4% of simeprevir-treated patients, and in 0% of placebo-treated patients. Two deaths occurred during the entire treatment phase (1 in each group)

2. What is the clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 2 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone?

There was no evidence found on the clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 2 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone.

3. What is the clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 3 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone?

There is no evidence found on the clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 3 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone.

4. What is the clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 4 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone?

There is no evidence found on the clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 4 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone.

Limitations

Data on the efficacy and safety of simeprevir plus PR compared to PR alone in patients with chronic hepatitis C genotype 1 who have had an inadequate response to prior PR therapy were limited to two phase II and one phase III trial. There was lack of data on sofosbuvir and other DAA medications, and on patients with genotypes 2, 3, or 4. In addition, one study²⁸ used a dosage of simeprevir and a duration of therapy that was not consistent with the Health Canada approved dose, so generalizability of the study to a Canadian context is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited data have shown that the addition of simeprevir to PR in patients with chronic hepatitis C genotype 1 who have had an inadequate response to prior PR therapy was more efficacious than PR alone in reducing SVR and was generally well tolerated.

More studies on sofosbuvir in this population, and in patients with chronic hepatitis C genotypes 2, 3, or 4 are needed.

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health

Tel: 1-866-898-8439

www.cadth.ca

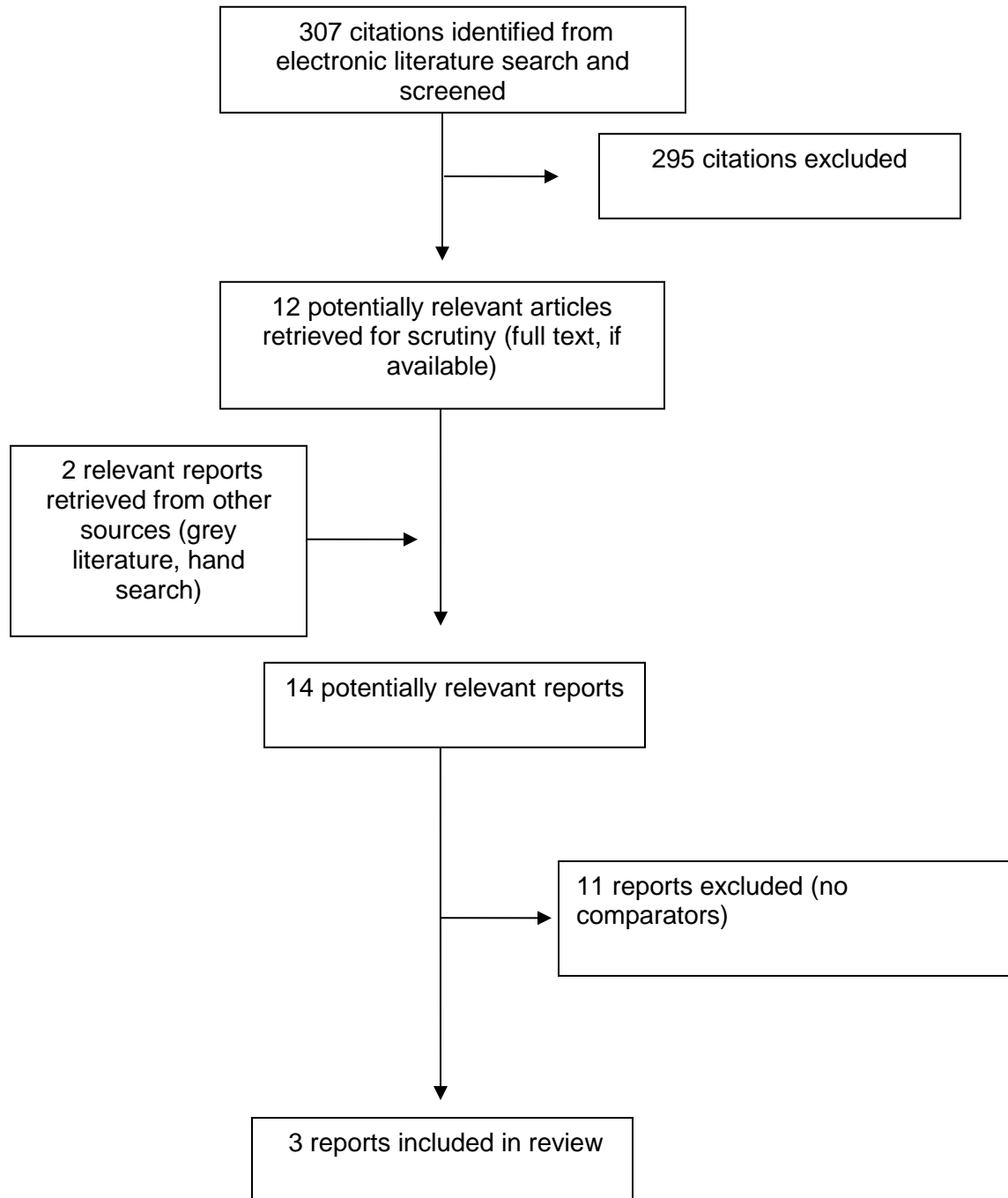
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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study design; Length of follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Main study outcomes
Manns ²⁸ 2011, Germany, Poland, UK, the Netherlands, Belgium, Ireland, France, USA	Phase IIa RCT; 28 days treatment. Outcomes measured at end of 28 days of treatment	HVC genotype-1 treatment-naïve (n = 74) and treatment-experienced patients (non-responders and prior relapsers to PR therapy) (n = 37)	Simeprevir 75, 150 or 200mg once a day + PR (n = 28 including 9 patients on simeprevir 75mg, 9 patients on simeprevir 150 mg, 10 patients on simeprevir 200 mg/day)	Placebo + PR (n = 9)	Decline in HCV RNA Adverse events Treatment discontinuation rate
Zeuzem ²⁹ 2014, Germany, New Zealand, Austria, UK, France, Russia, Belgium, USA	Phase IIb RCT; 48 weeks of treatment. Outcomes measured at 24 weeks after end of treatment	HVC genotype-1 treatment-experienced patients (non-responders and prior relapsers to PR therapy) (n = 462)	Simeprevir 100, or 150 mg once a day for 12, 24, or 48 weeks + PR for 48 weeks	Placebo + PR for 48 weeks	Sustained virologic response (SVR) Adverse events Treatment discontinuation rate
Forns ³⁰ 2014, Spain, Germany, New Zealand, France, Italy, Poland, UK, Belgium, USA	Phase III RCT; 48 weeks of treatment. Outcomes measured at 12 weeks after end of treatment	HVC genotype-1 treatment-experienced patients (relapsers after PR therapy) (n = 393)	Simeprevir 150 mg once a day + PR for 12 weeks, then PR alone for 12 or 36 weeks, based on response-guided therapy criteria	Placebo + PR for 12 weeks, then PR alone for 36 weeks	Sustained virologic response (SVR) On-treatment failure (non-responders) Relapse rate Rates of patients on simeprevir + PR who can shorten therapy Adverse events Treatment discontinuation rate

HCV: hepatitis C virus; PR: peginterferon-α and ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid

Appendix 3: Summary of Critical Appraisal of Included Studies

Table A2: Summary of Critical Appraisal of Included Studies		
First Author, Publication Year	Strengths	Limitations
Critical appraisal of included trials (Downs and Black²⁷)		
Manns ²⁸ 2011	<ul style="list-style-type: none"> hypothesis clearly described patients randomized main outcomes, interventions, patient characteristics, and main findings clearly described losses to follow-up described 	<ul style="list-style-type: none"> estimates of random variability and actual probability values not provided unable to determine if study power is sufficient to detect a clinically important effect
Zeuzem ²⁹ 2014	<ul style="list-style-type: none"> hypothesis clearly described patients randomized main outcomes, interventions, patient characteristics, and main findings clearly described estimates of random variability and actual probability values provided losses to follow-up described 	<ul style="list-style-type: none"> unable to determine if study power is sufficient to detect a clinically important effect
Forns ³⁰ 2014	<ul style="list-style-type: none"> hypothesis clearly described patients randomized main outcomes, interventions, patient characteristics, and main findings clearly described estimates of random variability and actual probability values provided losses to follow-up described study power is sufficient to detect a clinically important effect 	<ul style="list-style-type: none"> No major limitations identified

Appendix 4: Main Study Findings and Authors' Conclusions

Table A3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 ((clinical effectiveness and safety of simeprevir and/or sofosbuvir combined with peginterferon + ribavirin (PR) in patients with chronic hepatitis C genotype 1 who have had an inadequate response to prior direct acting antiviral (DAA) plus (PR) therapy or prior treatment with PR alone))		
Manns ²⁸ 2011	<p>18/28 patients treated on simeprevir + PR (9/9 prior relapsers and 9/19 non-responders) had HCV RNA < 25 IU/ml at day 28</p> <p>0/9 patients treated with placebo + PR had HCV RNA < 25 IU/ml at day 28</p> <p>Patients on 150 or 200 mg doses had better HCV RNA decline than those on 75 mg dose. Similar results between 150 and 200 mg doses.</p> <p>Adverse events rates: 8/9 patients on placebo + PR (88.9%) 8/9 patients on simeprevir 75 mg/day + PR (88.9%) 9/9 patients on simeprevir 150 mg + PR (100%) 10/10 patients on simeprevir 200 mg + PR (100%) Most adverse events were grade 1 or 2 No treatment discontinuation in any group</p>	<p><i>"Once daily TMC435 with P/R showed potent, dose-dependent antiviral activity over 28 days, and had a favourable tolerability profile" (p 1021)</i></p>
Zeuzem ²⁹ 2014	<p>SVR rates at 24 weeks after end of treatment: significantly higher in groups on simeprevir + PR than those on placebo + PR (61% - 80% vs 23%; $P < 0.001$)</p> <p>SVR rates at 24 weeks after end of treatment: In patients with null response: 37.5% - 58.8% in simeprevir group (18.8% in placebo group) (P value not reported)</p> <p>In patients with partial response: 47.8% - 86.4% in simeprevir group (8.7% in placebo group) (P value not reported)</p> <p>In patients with relapsers: 76.9% - 88.9% in simeprevir group (37.0% in placebo group) (P value not reported)</p> <p>All groups had similar adverse event rates (total percentage not reported). Most adverse events were grade 1 or 2. Permanent discontinuation in 8.8% of simeprevir-treated patients, 4.5% in placebo-treated patients.</p>	<p><i>"In treatment-experienced patients, 12, 24, or 48 weeks simeprevir (100 mg or 150 mg once daily) in combination with 48 weeks PegIFN and RBV significantly increased rates of SVR at 24 weeks compared with patients given placebo, PegIFN, and RBV and was generally well tolerated" (p 430)</i></p>
Forns ³⁰ 2014	<p>SVR rates at 12 weeks after end of treatment: significantly higher in groups on simeprevir + PR than those on placebo + PR (79.2% vs 36.1%; $P < 0.001$)</p> <p>On-treatment failure (non-responders): significantly lower in groups on simeprevir + PR than those on placebo + PR (3.1% vs 27.1%; $P < 0.001$)</p> <p>Relapse rates: significantly lower in groups on simeprevir + PR than those on placebo + PR (18.5% vs 48.4%; $P < 0.001$)</p> <p>Most patients on simeprevir + PR (92.7%) were able to shorten therapy to 24 weeks</p> <p>Adverse events: Similar adverse event rates between simeprevir + PR and</p>	<p><i>"In a phase 3 trial of patients who had relapsed after interferon-based therapy, the addition of simeprevir to PR was generally well tolerated, with an SVR12 rate of 79.2%. Most patients (92.7%) receiving simeprevir were able to shorten therapy to 24 weeks" (p 1669)</i></p>

Table A3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	Main Study Findings	Authors' Conclusions
	placebo + PR (97.3% in simeprevir + PR group, 94.0% in placebo + PR group had any adverse events) Most adverse events were grade 1 or 2 Permanent discontinuation in 0.4% of simeprevir-treated patients, and in 0% of placebo-treated patients. Two deaths occurred during the entire treatment phase (1 in each group)	
Research question 2 (clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 2 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone)		
The literature search did not find clinical evidence for this research question		
Research question 3 (clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 3 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone)		
The literature search did not find clinical evidence for this research question		
Research question 4 (clinical effectiveness and safety of simeprevir and/or sofosbuvir and PR combination treatments in patients with chronic hepatitis C genotype 4 who have had an inadequate response to prior DAA plus PR therapy or prior treatment with PR alone)		
The literature search did not find clinical evidence for this research question		

HCV: hepatitis C virus; PR: peginterferon- α and ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid