TITLE: Interferon-free Regimens for Genotype 1 Chronic Hepatitis C: A Review of the Clinical Evidence and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES

In Canada it is estimated that 242,000 Canadians have chronic hepatitis C virus (HCV) infection; however, the exact number affected is unknown as 30% to 70% of patients are unaware that they are infected.[1,2] Fifteen to 25% of patients with chronic infection will develop hepatocellular carcinoma, progressive liver disease, end-stage liver disease, or will require a liver transplant over 20 to 30 years of infection.[3,4] There are six major HCV genotypes,[5] and genotype 1 accounts for approximately 60% of HCV infections in Canadians.[6]

Since the early 2000s, the standard of care has been a combination of pegylated interferon alpha plus ribavirin (PR).[5] The goal of treatment is viral eradication, defined as sustained virological response (SVR).[7,8] Approximately 50% of patients with genotype 1 chronic hepatitis C (CHC) can expect to achieve SVR with PR therapy.[5] Since 2011 four direct-acting antiviral agents (DAA) have been authorized to be used in combination with PR for the treatment of patients with genotype 1 CHC.[5] Using triple therapy of DAA in combination with PR significantly increases SVR rates when compared with the use of PR alone.[5] Patients receiving interferon may experience side effects such as fatigue, flu-like symptoms, psychiatric symptoms, seizures, weight loss, peripheral neuropathy, and bone marrow suppression.[5]

A number of novel DAA regimens, many of which do not include interferon, are currently under investigation and may be approved by Health Canada in the near future. Early evidence suggests that these treatments may offer better side effect profiles and higher cure rates, but may offer additional challenges in terms of affordability and accessibility. The purpose of this report is to provide evidence on the clinical effectiveness and cost-effectiveness of any interferon-free combination including at least one of the following drugs: boceprevir, telaprevir, simeprevir (SIM), or sofosbuvir (SOF).

RESEARCH QUESTIONS

1. What is the evidence for the clinical effectiveness and safety of boceprevir, simeprevir, sofosbuvir, and telaprevir interferon-free regimens?

2. What is the cost-effectiveness of boceprevir, simeprevir, sofosbuvir, and telaprevir interferon-free regimens?

KEY FINDINGS

The available evidence from the clinical trials indicates that sustained virological response (SVR) was achieved by more than 90% of patients who received sofosbuvir (SOF) and ledipasvir (LDV) with or without ribavirin (RBV) for 8, 12 or 24 weeks; SOF and daclatasvir (DCV) with or without RBV for 12 or 24 weeks; SOF and GS-9669 plus RBV for 12 weeks in treatment naïve and treatment experienced patients. Lower rates of SVR were reported in those who only received SOF plus RBV. Serious AEs and discontinuation due to AEs were low and anemia, rash and depression were low in patients who did not receive RBV. LDV, DCV and GS-9669 have not yet received Health Canada Notice of Compliance (NOC).

Two economic evaluations conducted outside of Canada demonstrated that SOF plus simeprivir (SIM) is more cost-effective than SOF plus RBV. However, cost-effectiveness of SOF plus SIM in a Canadian population is uncertain.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Ovid Medline, Ovid EMBASE, The Cochrane Library (2014, Issue 5), 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. The search was limited to English language documents published between Jan 1, 2011 and May 28, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, selected potentially relevant articles for retrieval of full-text publications for further investigation and evaluated the full-text publications for final selection, according to the criteria listed in Table 1.

Table 1: Selection Criteria

Population	Patients with CHC genotype 1 infection
Intervention	Any interferon-free combination including at least one of the following drugs: boceprevir, telaprevir, simeprevir, or sofosbuvir (e.g., simeprevir + sofusbuvir, sofosbuvir + ribavirin, ledipasvir + sofosbuvir, daclatasvir + sofosbuvir)
Comparator	None specified

Outcomes	Clinical effectiveness (e.g. SVR) Safety Cost-Effectiveness
Study Designs	Health technology assessment (HTA), systematic review (SR) and meta-analysis (MA), randomized controlled trial (RCT), non-randomized studies (Non-RCTs), and economic evaluation

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2011. Studies were excluded if they were included in at least one of the included systematic reviews.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews, network meta-analysis, trials (RCTs and non-randomized studies), and cost evaluations was assessed using AMSTAR,[9] ISPOR Checklist,[10] Downs and Black,[11] and Drummond checklists,[12] respectively. Numeric scores were not calculated. Instead, the strengths and limitations of the studies are summarized.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 545 citations. After screening titles and abstracts, 522 articles were excluded and 23 potentially relevant articles were selected for full-text review. Five relevant citations were identified from the grey literature. Of these 28 reports, 18 did not meet the inclusion criteria and were excluded, leaving a total of 10 relevant reports, one of which was a health technology assessment,[13] seven non-RCTs[14-21] of which two reports included results from one unique study which comprised randomized and non-randomized groups,[20,21] and one economic evaluation.[22] The study selection process is outlined in Appendix 1. Additional references of potential interest are provided in the Appendix 5.

Summary of Study Characteristics

Characteristics of the included health technology assessment, clinical trials and economic evaluation are summarized below and details are provided in Appendix 2.

Health technology assessment

A single health technology assessment (HTA) by Tice et al.[13] of the Institute for Clinical and Economic Review was identified for this review. Two studies were included in this HTA that specifically examined interferon-free regimens (SOF plus SMV with or without ribavirin for treatment naïve and treatment experienced patients, and SOF plus RBV in treatment naïve patients). Patients with CHC infection with genotypes 1, 2 and 3 who are treatment naïve or treatment experienced were included. This HTA focused on regimens incorporating SIM and SOF and compared them with the combination of PR and one of the first generation protease inhibitors (telaprevir or boceprevir) for patients with genotype 1. In addition, the combination of SOF and ribavirin (RBV) was compared to PR in patients with genotype 2 or genotype 3, and

finally they examined the combination of SOF plus RBV or SOF plus SIM in comparison to no treatment in patients who are interferon-ineligible or intolerant. A network meta-analysis (NMA) and a health economic evaluation were conducted to compare different treatment regimens. The NMA was based on a systematic review of clinical trials. In order for a study to be included in the NMA, a treatment regimen with dosing similar to the final FDA indications must have been received by at least one study group. The economic evaluation compared SIM plus SOF or SOF plus RBV with no treatment in patients who have chronic HCV genotype 1 infection, treatment naïve or previously treated and are interferon ineligible or intolerant. Data used were obtained from clinical trials. The expenses included costs of drugs, costs of liver-related complications, and costs of maintenance care. Costs were discounted at 3% and prices were in US dollars. Outcomes of interest in this HTA were SVR, adverse effects, and cost per SVR.

Clinical Studies

Seven clinical trials assessing SOF interferon-free regimens were identified.[14-21] Five studies[15-19] included patients from the US only, one study (reported in two publications)[20,21] enrolled patients from New Zealand only, and one study[14] enrolled patients from the US, France, Germany, Italy, Spain, Puerto Rico, and the UK. Six studies[14,15,17-21] included patients with chronic HCV genotype 1 infection who were treatment naïve; in two of these studies[15,17] patients were treatment naïve and without cirrhosis, three[17,18,20,21] also included patients who were previously treated either with protease inhibitors (PI) or with PR. One study[16] included treatment experienced patients only. The number of recruited patients in these studies ranged from 60 to 865. Even though in most of these trials treatments were allocated by randomization, there was no control group who received no treatment or an interferon-based regimen. Treatments assessed in these clinical trials were combination of SOF plus RBV, or a fixed-dose combination of SOF and ledipasvir (LDV) with or without RBV, or SOF plus daclatasvir (DCV) with or without RBV, or SOF and GS-9669 plus RBV. Treatment durations in these trials ranged between 6 weeks to 24 weeks with follow-up ranging between 12 and 24 weeks after the end of therapy. Sustained virological response at 12 weeks or at 24 weeks after the end of therapy was reported in all the trials, as well as safety.

Cost-Effectiveness

A recent economic evaluation was conducted in the US to evaluate the cost-effectiveness of SOF plus SIM in comparison with SOF plus RBV.[22] Patients included in this analysis were assumed to have chronic HCV genotype 1 infection, treatment naïve or previously treated and are interferon-ineligible or interferon intolerant. Data used were obtained from clinical trials. The expenses included costs of a new patient visit, initial HCV screening, genotype assay, noninvasive fibrosis staging, drugs, medical monitoring and treatment related adverse events. Costs and quality-adjusted life years (QALYs) were discounted at 3%. Prices were in US dollars. The clinical effectiveness was assessed using QALYs.

Summary of Critical Appraisal

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

Health technology assessment

The NMA reported in the HTA by Tice et al.[13] was assessed using ISPOR criteria.[10] According to ISPOR criteria, the SR had methodological issues. The method of study selection and data

extraction was not reported and it is unclear whether it was conducted by more than one author. In addition, the list of excluded studies was not provided and the literature search was limited to SIM and SOF. Only phase 3 trials of telaprevir and boceprevir were included and these studies were identified using published systematic reviews. Characteristics of included studies for telaprevir and boceprevir were not reported. Finally, the quality of included studies was not assessed. The NMA was conducted using frequentist estimation procedures implemented in Stata version 13.1. The outcome measurements were appropriate. Only indirect estimates of effect were provided. Heterogeneity and inconsistency were not assessed. Publication bias was not assessed. Data from single arm trials were included in the analysis. There was no indirect comparison between different interferon-free regimens.

The economic evaluation was considered to be of good methodological quality according to the Drummond checklist. The research question was well defined and the analysis method was clearly stated. The key parameters on which the analysis was based were justified and the time horizons were clearly specified. Discount rate was reported. Few limitations were identified: no sensitivity analyses were performed; the cost per additional SVR was reported by looking exclusively at the initial treatment course, hence no cost effectiveness results were reported at time horizons, 1 year, 5 years, and 20 years. Efficacy data used for SOF plus RBV was pooled from two studies with one of the studies not defined in the report. In addition, for treatment experienced patients, SVR for SOF plus RBV was estimated from the pooled estimate in treatment naïve patients. It is not clear how the SVR rates used in the economic model were derived. Interferon-free regimens were only compared with no treatment.

Clinical Studies

All seven clinical trials[14-21] clearly stated the objective and the selection criteria and described patient characteristics, interventions and outcomes. All seven trials stated that they had an open-label design with patients and investigators were not masked to treatment allocation, however three clinical trials[14-16] indicated that post treatment HCV RNA results were blinded to the investigator and sponsor. A sample size calculation was reported in four clinical trials.[14-16,19] No power calculation was reported for the other three clinical trials.[17,18,20,21] Five clinical trials[14,15,17-19] reported results using either intention-to-treat analyses or including all the patients who underwent randomization and received treatment in the analyses. The proportion of patients who discontinued treatment due to adverse events ranged between 0% and 5%. Generalizability was uncertain as to whether the study patients were representative of all patients.

Cost-Effectiveness

The economic evaluation report[22] was considered to be of high methodological quality according to the Drummond checklist. The research question was well defined and the analysis method was clearly stated. The key parameters on which the analysis was based were justified and the time horizons were clearly specified. Sensitivity analyses were performed and variables were justified. The generalizability of the study results to Canadian setting is uncertain due to the differences in costs and health care systems between Canada and the US.

Summary of Findings

The overall findings are summarized below and detailed findings from the individual clinical studies are provided in Appendix 4.

What is the evidence for the clinical effectiveness and safety of boceprevir, simeprevir, sofosbuvir, and telaprevir interferon-free regimens?

Health technology assessment

Effectiveness

The HTA by Tice et al.[13] identified two studies which reported results of interferon-free regimens. It was estimated that in treatment naïve patients, more than 90% who received SOF plus SIM achieved SVR, while 47% of those who received 12 weeks of SOF plus RBV achieved SVR. In patients who are treatment experienced, 90% of those who received SOF plus SIM had SVR and no SVR was reported for those who received SOF plus RBV

Safety

No safety data was reported in this HTA for patients who received interferon-free regimen.

Clinical Studies

Effectiveness

In treatment naïve patients, 95 to 99% of those who received LDV and SOF for 12 weeks, achieved SVR12.[14,15,17] SVR12 was achieved by 97 to 100% of patients who received LDV and SOF plus RBV for 12 weeks.[14,20] SVR12 was achieved by 98% and 99% of patients who received LDV and SOF for 24 weeks or LDV and SOF plus RBV for 24 weeks, respectively.[14] In patients who received LDV and SOF with or without RBV for 8 weeks, SVR12 occurred in 93% to 100% of patients.[15,17] Sixty-eight percent of patients who received LDV and SOF plus RBV for 6 weeks achieved SVR. SVR24 rates of a 24-week regimen of SOF and weight-based or low-dose RBV were 68% and 48%, respectively.[19] On the other hand, 84% of patients who received SOF and weight-based RBV for 12 weeks achieved SVR12.[21] All patients who received SOF for 7 days, then SOF and daclatasvir (DCV) for 23 weeks, or DCV and SOF for 24 weeks, or DCV and SOF plus RBV for 24 weeks, or DCV and SOF for 12 weeks achieved SVR12, and 95% of those who received DCV and SOF plus RBV for 12 weeks achieved SVR 12.[18] Finally SVR 12 was achieved by 92% of those who received SOF plus GS-9669 plus RBV for 12 weeks. [20]

In treatment experienced patients, those who received LDV and SOF for 12 weeks, SVR12 was achieved by 94 to 95% of patients.[16,17] For patients who were cirrhotic and received LDV and SOF for 12 weeks, 70% achieved SVR 12, while 100% of patients who were cirrhotic and received LDV and SOF plus RBV for 12 weeks achieved SVR12.[20] Patients who received LDV and SOF plus RBV for 12 weeks, SVR12 was achieved by 96 to 100% of them.[16,17,20] Most (95% to 100%) patients who received LDV and SOF with or without RBV for 24 weeks or SOF plus GS-9669 plus RBV for 12 weeks or DCV and SOF with or without RBV for 24 weeks achieved SVR12.[16,18,20] Finally, 10% of patients who received SOF plus RBV for 12 weeks achieved SVR 12.[21]

Safety

The proportions of patients who experienced a serious adverse event (SAE) ranged between 0% and 8%, with the highest proportion of SAEs was reported in patients who received LDV plus SOF for 24 weeks.[14] The proportion of patients who discontinued treatment due to adverse

events ranged from 0% to 3%, with the highest rate reported in patients who received LDV plus SOF plus RBV for 24 weeks.[14] Anemia rates ranged from 0% to 1% in those who received RBV free regimen, while in those who received RBV, anemia rates ranged from 8% in those who received LDV plus SOF plus RBV for 8 weeks[15] to 32% in those who received SOF plus weight based RBV for 24 weeks.[19] Rash rate ranged from 0% to 30%, with the highest rate reported in those who received SOF plus RBV for 12 weeks.[21] Depression was only reported in one study by Gane et al.[20] and the rate of depression ranged from 0% to 22% with higher rates reported in those who received LDV plus SOF plus RBV for 12 weeks.

What is the cost-effectiveness of boceprevir, simeprevir, sofosbuvir, and telaprevir interferon-free regimens?

Cost-Effectiveness

The HTA by Tice et al.[13] reported that cost per additional SVR in patients who receive SOF plus SIM is US$172,000 for both treatment naïve and treatment experienced patients. In patients who received SOF plus RBV, the cost per additional SVR was US$245,000 in treatment naïve patients and US$289,000 in treatment experienced patients.

In the Hagan et al.[22] cost analysis, patients who received SIM plus SOF, the cost per QALY and cost per SVR would be US$11,255 and US$170,456 respectively which is lower than the cost per QALY and cost per SVR of SOF plus RBV (US$16,857 and US$262,046 respectively). This economic evaluation indicates that in comparison with SOF plus RBV a cost saving per SVR of US$91,590 would be achieved if SIM plus SOF was used.

Limitations

The HTA reported limited data on interferon-free regimens, and included limited number of clinical trials for the estimation of clinical effectiveness and cost-effectiveness. In addition, no safety data were reported for patients who received interferon-free regimens in the HTA.

All of the included clinical trials were open label. Most of the included clinical trials were of small sample size and power was not calculated or described. When reported, historical control rate was used to calculate power and sample size for the trials. None of the trials included control arms, as all trials investigated different treatment combinations of SOF plus LDV or SOF plus DCV or SOF plus GS-9669 with or without RBV for different durations, and none of the trials did a comparison between different treatment arms. None of the trials compared interferon-free regimens with a triple therapy of SIM or SOF or boceprevir or telaprevir plus PR. LDV, DCV and GS-9669 have not yet received Health Canada Notice of Compliance (NOC).

Adverse effects, especially depression, were insufficiently reported. In addition, adverse events in the trials with small sample sizes might overestimate or underestimate rates of adverse events.

None of the clinical trials or economic evaluations were conducted in Canada, so applicability to the Canadian setting is unclear. In addition, no economic evaluation comparing SIM plus SOF with SOF plus LDV or SOF plus DCV or SOF plus GS-9669 was identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

SVR was achieved by more than 90% of patients who received LDV and SOF with or without RBV for 8, 12 or 24 weeks, DCV and SOF with or without RBV for 12 or 24 weeks, GS-9669 plus RBV for 12 weeks in treatment naïve and treatment experienced patients. Even in treatment-experienced cirrhotic patients who are usually difficult to treat, 100% of patients who received LDV and SOF plus RBV for 12 weeks achieved SVR12. A lower rate of SVR was noticed in those who received SOF plus RBV. Serious AEs and discontinuation due to AE were low, and anemia, rash and depression (commonly seen in patients who receive interferon regimens) were low in patients who did not receive RBV.

No studies reporting results for interferon-free regimens that included boceprevir and telaprevir were identified.

Two economic evaluations conducted outside of Canada demonstrated that SOF plus SIM is more cost-effective than SOF plus RBV.

Patients with chronic infection may develop hepatocellular carcinoma, progressive liver disease, end-stage liver disease, or will require a liver transplant over 20 to 30 years of infection. Patients receiving interferon could experience side effects such as fatigue, flu-like symptoms, psychiatric symptoms, seizures, weight loss, peripheral neuropathy, and bone marrow suppression. Evidence from interferon-free clinical trials indicate high SVR rate and low adverse events rates, however no head to head clinical trial comparing interferon-free regimens with regimens that include interferon was identified, making it difficult to compare such regimens. Randomized studies directly comparing interferon-free regimens with interferon based regimens are required to further inform choices made by physicians, health authorities and to provide stronger evidence for guidelines.

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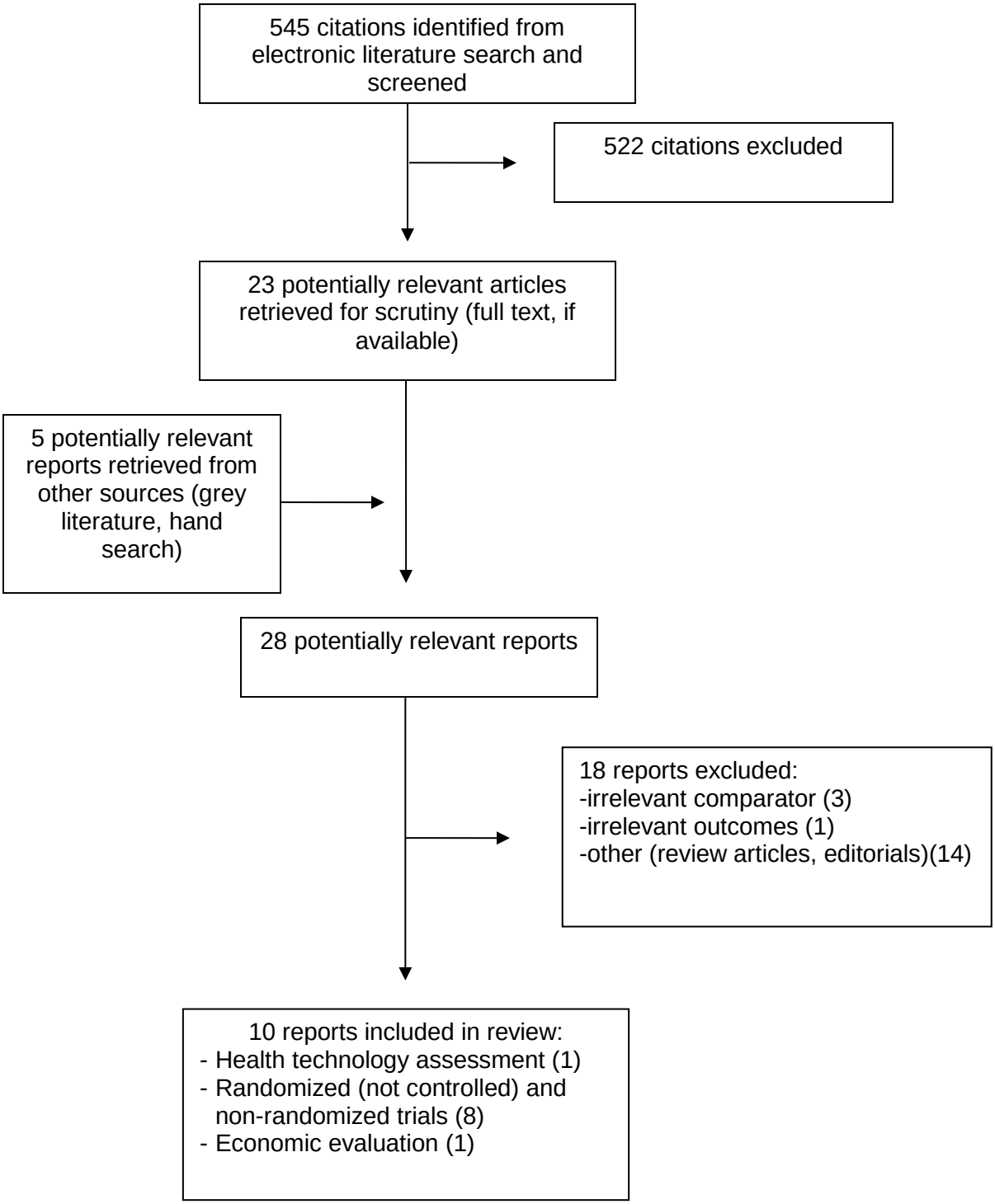
APPENDIX 1: Selection of Included Studies



APPENDIX 2: SUMMARY OF STUDY CHARACTERISTICS

Table A2.1: Characteristics of Included Heath Technology Assessment

First Author, Publication Year, Country	Study Design	Population	Intervention	Comparator	Outcomes
Tice,[13] 2014, US	HTA (assessed clinical and cost effectiveness). time horizons for the cost effectiveness model were: 1 year, 5 years, and 20 years	Patients with chronic HCV who are treatment naïve or treatment experienced			SVR 12, Adverse effects, cost per SVR
		and with genotypes 1	SIM, or SOF	Telaprevir + PR, or boceprevir + PR	
		or with genotype 2 or genotype 3	SOF + ribavirin	PR	
		or interferon-ineligible or intolerant	SOF + ribavirin, or SOF + SIM	No treatment	
HCV=hepatitis C Virus; HTA=Health Technology Assessment; SIM= Simeprevir; SOF= Sofosbuvir; SVR 12=sustained virological response 12 weeks after the end of treatment; US=the United States of America					

Table A2.2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study design, length of follow-up	Patient characteristics, sample size	Interventions	Outcomes
Non-RCTs				
Afdhal,[14] 2014, US, France, Germany, Italy, Spain, Puerto Rico, and UK	open-label, randomized trial, Parallel Assignment, Treatment duration: 12 weeks or 24 weeks; follow up: 12-weeks after the end of therapy.	patients with chronic HCV genotype 1 infection who are treatment naïve n=865	LDV 90 mg and SOF 400 mg orally one daily for 12 weeks, n=214; LDV 90 mg and SOF 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 12 weeks, n=217; LDV 90 mg and SOF 400 mg orally once daily for 24 weeks, n=217; LDV 90 mg and SOF 400 mg orally once daily + RBV	SVR 12 Safety

First Author, Publication Year, Country	Study design, length of follow-up	Patient characteristics, sample size	Interventions	Outcomes
			(determined according to body weight) orally twice daily for 24 weeks, n=217	
Kowdley,[15] 2014, US	open-label, randomized trial, Parallel Assignment, Treatment duration: 8 weeks or 12 weeks; follow up: 12-weeks after the end of therapy.	patients with chronic HCV genotype 1 infection who are treatment naïve and who are without cirrhosis n=647	LDV 90 mg and SOF 400 mg orally once daily for 8 weeks, n=215; LDV 90 mg and SOF 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 8 weeks, n=216; LDV 90 mg and SOF 400 mg orally once daily for 12 weeks, n=216;	SVR 12 Safety
Osinusi,[19] 2013, US	open-label, one group with 2 arms were randomized, Parallel Assignment, another group with 1 arm was not randomized, Treatment duration: 24 weeks; follow up: 24-weeks after the end of therapy.	patients with chronic HCV genotype 1 infection who are treatment naïve, n=60	<u>Patients with early to moderate liver fibrosis:</u> SOF 400 mg orally once daily + RBV (determined according to body weight) orally once or twice daily for 24 weeks, n=10 <u>Patients with all stages of liver fibrosis:</u> SOF 400 mg orally once daily + RBV (determined according to body weight) orally once or twice daily for 24 weeks, n=25 SOF 400 mg orally once daily + RBV 600 mg orally once daily for 24 weeks, n=25	SVR 24 Safety
Lawitz,[17] 2014, US	open-label, randomized trial, Parallel Assignment, Treatment duration: 8 weeks or 12 weeks; follow up: 24-weeks	patients with chronic HCV genotype 1 infection who are treatment naïve and who are without cirrhosis, n=60, and patients	<u>treatment naïve patients:</u> LDV 90 mg and SOF 400 mg orally once daily for 8 weeks, n=20; LDV 90 mg and SOF 400 mg orally once daily + RBV (determined according to body weight) orally in a divided daily	SVR 12, SVR 24 Safety

First Author, Publication Year, Country	Study design, length of follow-up	Patient characteristics, sample size	Interventions	Outcomes
	after the end of therapy.	who are previously treated with PI, n=40	dose for 8 weeks, n=21; LDV 90 mg and SOF 400 mg orally once daily for 12 weeks, n=19; <u>treatment experienced patients:</u> LDV 90 mg and SOF 400 mg orally once daily for 12 weeks, n=19; LDV 90 mg and SOF 400 mg orally once daily + RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=21	
Sulkowski,[18] 2014, US	open-label, randomized trial, Parallel Assignment, Treatment duration: 12 weeks or 24 weeks; follow up: 12-weeks after the end of therapy.	patients with chronic HCV genotype 1 infection who are treatment naïve, n=126, and patients who are previously treated with telaprevir or boceprevir +PR, n=41	<u>treatment naïve patients:</u> SOF 400 mg for 7 days, then SOF 400 mg and DCV 60 mg for 23 weeks, n=15; DCV 60 mg and SOF 400 mg for 24 weeks, n=14; DCV 60 mg and SOF 400 mg plus RBV for 24 weeks, n=15; DCV 60 mg and SOF 400 mg for 12 weeks n=41; DCV 60 mg and SOF 400 mg plus RBV for 12 weeks, n=41; <u>treatment experienced patients:</u> DCV 60 mg and SOF 400 mg for 24 weeks, n=21; DCV 60 mg and SOF 400 mg plus RBV for 24 weeks,n=20	SVR 12, SVR 24 Safety

First Author, Publication Year, Country	Study design, length of follow-up	Patient characteristics, sample size	Interventions	Outcomes
Gane,[21] 2013, New Zealand	open-label, non-randomized trial, Treatment duration: 12 weeks; follow up: 24-weeks after the end of therapy.	patients with chronic HCV genotype 1 infection who are treatment naïve, n=25, and patients who are previously treated with PR, n=10	SOF 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 8 weeks, n=10	SVR 12 SVR 24 Safety
Gane,[20] 2014, New Zealand	open-label, included randomized and non-randomized arms, Treatment duration: 6 weeks; follow up: 24-weeks after the end of therapy.	patients with chronic HCV genotype 1 infection who are treatment naïve, and patients who are previously treated	<u>treatment naïve patients:</u> LDV 90 mg and SOF 400 mg orally once daily + RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=25 SOF 400 mg + GS-9669 500 mg once daily+ RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=25 fixed-dose combination of SOF 400 mg and LDV 90 mg + RBV (determined according to body weight) orally in a divided daily dose for 6 weeks, n=25 <u>treatment experienced patients:</u> LDV 90 mg and SOF 400 mg orally once daily + RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=9 SOF 400 mg and GS-9669 500 mg once daily+ RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=10	SVR 12 Safety

First Author, Publication Year, Country	Study design, length of follow-up	Patient characteristics, sample size	Interventions	Outcomes
			prior null responders with cirrhosis: fixed-dose combination of SOF 400 mg and LDV 90 mg orally once daily 12 weeks, n=10 fixed-dose combination of SOF 400 mg and LDV 90 mg orally once daily + RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=9	
Afdhal,[16] 2014, US	open-label, randomized trial, Parallel Assignment, Treatment duration: 8 weeks or 12 weeks; follow up: 24-weeks after the end of therapy.	patients with chronic HCV genotype 1 infection who are previously treated with PI or PR, n=440	LDV 90 mg and SOF 400 mg orally once daily for 12 weeks, n=109; LDV 90 mg and SOF 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 12 weeks, n=111; LDV 90 mg and SOF 400 mg orally once daily for 24 weeks, n=109; LDV 90 mg and SOF 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 24 weeks, n=111	SVR 12, SVR 24 Safety

HCV=hepatitis C Virus; DCV=daclatasvir; LDV=Ledipasvir; PI=protease inhibitors; PR=pegylated interferon alfa plus ribavirin; RBV=Ribavirin; SOF=Sofosbuvir; SVR 12=sustained virological response 12 weeks after the end of treatment; UK=the United Kingdom; US=the United States of America

Table A2.3: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Study Design, Time horizon	Patient Characteristics	Intervention/ Comparators	Assumptions
Hagan,[22] 2014, US	Cost effectiveness analysis lifetime horizon	patients with chronic HCV genotype 1 infection who are treatment naïve or previously treated and who are interferon-ineligible or interferon intolerant	SIM + SOF SOF + RBV	90% of subjects who were not cured with initial treatment (SOF+SMV or SOF+RBV) were retreated with rescue therapy
HCV=hepatitis C Virus; RBV=Ribavirin; SIM=Simeprevir; SOF=Sofosbuvir; SVR=sustained virological response; US=The United States of America				

APPENDIX 3: SUMMARY OF STUDY STRENGTHS AND LIMITATIONS

Table A3.1: Summary of Critical Appraisal of Included Heath Technology Assessment

First Author, Publication Year, Country	Strengths	Limitations
Tice,[13] 2014, US	Network meta-analysis assessed with ISPOR checklist: • The rationale and the objectives for the study were clearly described • The NMA was based on a systematic review to identify all relevant studies of SOF and SIM. • List of included studies was provided • The analysis was conducted using frequentist estimation procedures implemented in Stata version 13.1. • outcome measurements were appropriate	• List of excluded studies not provided • Publication bias was not assessed. • Data from single arm trials were included in the analysis. • Only phase 3 trials of telaprevir and boceprevir were included • Characteristics of included studies for telaprevir and boceprevir were not reported. • quality of included studies was not assessed • Only indirect estimates of effect were provided • Heterogeneity and inconsistency were not assessed • It is not clear if study selection and data extraction performed by more than one reviewer • There was no indirect comparison between different interferon-free regimens.
	The economic evaluation was assessed using the Drummond's checklist.[12] • Clearly described purpose of the study • Resource use and costs were described and justified • time horizons were clearly specified • Discount rate was reported	• no sensitivity analyses were performed • cost per additional SVR was reported by looking just at the initial treatment course • no cost effectiveness results were reported at time horizons, 1 year, 5 years, and 20 years • No detailed information on effectiveness inputs were provided for interferon-free regimens. • Interferon-free regimens were only compared versus no treatment
SIM=Simeprevir; SOF=Sofosbuvir; SVR=sustained virological response		

Table A3.2: Summary of Critical Appraisal of Included Clinical Studies

First Author, Publication Year, Country	Strengths	Limitations
Non-RCTs		
Afdhal,[14] 2014, US, France, Germany, Italy, Spain, Puerto Rico, and UK	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. An interactive Web and Voice Response System for the randomization procedure • Post treatment HCV RNA results were blinded to the Investigator and Sponsor. • Number discontinued or lost to follow up were reported • Choice of sample size was justified. • intent-to-treat analysis was used • P-values provided	• SVR in each of the treatment groups were compared with an adjusted historical rate • No comparison was made between different treatment groups • Allocation was not described • Industry-sponsored study • patients and investigators were not masked to treatment allocation • lack of a control arms
Kowdley,[15] 2014, US	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. An interactive Web Response System for the randomization procedure • Post treatment HCV RNA results were blinded to the Investigator and Sponsor. • Number discontinued or lost to follow up were reported • Choice of sample size was justified. • intent-to-treat analysis was used • P-values provided	• SVR in each of the treatment groups were compared with an adjusted historical rate • Allocation was not described • Industry-sponsored study • patients and investigators were not masked to treatment allocation • lack of a control arms
Osinusi,[19] 2013, US	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. Randomization was done	• No comparison was done between all treatment arms • patients and investigators were not masked to treatment allocation • Patients received treatment without randomization in one of

First Author, Publication Year, Country	Strengths	Limitations
	using random numbers • Number discontinued or lost to follow up were reported • Choice of sample size was justified. • intent-to-treat analysis was used • P-values provided • Not sponsored by manufacturer	the treatment arms • lack of a control arms • small sample size
Lawitz,[17] 2014, US	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. Computerized random numbers were used for the randomization procedure. • Number discontinued or lost to follow up were reported • intent-to-treat analysis was used	• No comparison was made between different treatment groups • Allocation was not described • Industry-sponsored study • patients and investigators were not masked to treatment allocation • sample size was not powered to allow for comparison between groups • lack of a control arms • small sample size
Sulkowski,[18] 2014, US	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. • Number discontinued or lost to follow up were reported • intent-to-treat analysis was used	• No comparison was made between different treatment groups • Industry-sponsored study • patients and investigators were not masked to treatment allocation • randomization procedure was not described • Choice of sample size was not justified. • lack of a control arms • small sample size
Gane,[21] 2013, New Zealand	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Number discontinued or lost to follow up were reported	• No comparison was made between different treatment groups • Industry-sponsored study • patients and investigators were not masked to treatment allocation • No randomization was done, treatments were assigned to patients by their previous treatment experience

First Author, Publication Year, Country	Strengths	Limitations
		• No sample-size calculations were performed. • Not clear if intent-to-treat analysis was used • lack of a control arms • small sample size
Gane,[20] 2014, New Zealand	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Some treatment arms were randomized but, open label study. Computer generated randomization sequence for the randomization procedure • Number discontinued or lost to follow up were reported	• No comparison was made between different treatment groups • Industry-sponsored study • patients and investigators were not masked to treatment allocation • lack of a control arms • small sample size • No sample-size calculations were performed. • Not clear if intent-to-treat analysis was used • Not all patients were randomly assigned to treatments, as patients in some treatment arms were enrolled to receive treatment without randomization.
Afdhal,[16] 2014, US	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. An interactive Web and Response System for the randomization procedure • Post treatment HCV RNA results were blinded to the Investigator and Sponsor. • Number discontinued were reported • Choice of sample size was justified. • P-values provided	• No comparison was made between different treatment groups • SVR in each of the treatment groups were compared with an adjusted historical rate • Allocation was not described • Industry-sponsored study • patients and investigators were not masked to treatment allocation • lack of a control arms • Not clear if intent-to-treat analysis was used
SVR=sustained virological response; UK=the United Kingdom; US=the United States of America		

Table A3.3: Summary of Critical Appraisal of Included Economic Evaluations

First Author, Publication Year, Country	Strengths	Limitations
Hagan,[22] 2014, US	• Clearly described research question • Appropriately defined comparators • Provided detailed information on clinical inputs such as effectiveness • Resource use and costs were described • Perspective was clearly described (societal perspective) • In sensitivity analyses, the range or distribution of values were clearly described • Not sponsored by manufacturer • Time horizon was for lifetime • Both costs and QALYs were discounted	• The study was conducted using cost information from the US which may limit the generalizability to Canada
QALYs=quality-adjusted life years; US=The United States of America		

APPENDIX 4: MAIN STUDY FINDINGS AND AUTHORS' CONCLUSIONS

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">HTA/Systematic review/Meta-analysis</td></tr>
<tr><td>Tice,[13] 2014, US</td><td>

Main Findings:

<table>
<tr><th>Outcome</th><th colspan="2">treatment-naive patients</th><th colspan="2">treatment experienced patients</th></tr>
<tr><td></td><td>SOF +SIM</td><td>12-Wk SOF + RBV</td><td>SOF +SIM</td><td>12-Wk SOF + RBV</td></tr>
<tr><td>Efficacy</td><td colspan="4"></td></tr>
<tr><td>SVR12, n (%)</td><td>< 90%</td><td>47%</td><td>90%</td><td>NR</td></tr>
<tr><td colspan="5"></td></tr>
<tr><td>Efficacy</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Economic evaluation</td><td colspan="4"></td></tr>
<tr><td>Cost for initial treatment</td><td>$154,536</td><td>$176,352</td><td>$154,536</td><td>$176,352</td></tr>
<tr><td>Cost per additional SVR</td><td>$172,000</td><td>$245,000</td><td>$172,000</td><td>$289,000</td></tr>
</table>

Authors' Conclusion:

Therapeutic regimens containing SOF or SIM could substantially increase the number of patients achieving SVR relative to previous therapeutic options. In addition there is the added potential for SOF to provide the first effective interferon-free option to patients ineligible or intolerant to interferon. The benefits of SOF and SIM come at a substantially increased cost.

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<tr><td colspan="2">Non-RCTs</td></tr>
<tr><td>Afdhal,[14] 2014, US, France, Germany, Italy, Spain, Puerto Rico, and UK</td><td>

Main Findings:

<table>
<tr><th>Outcome</th><th>12-Wk LDV and SOF (N=214)</th><th>12-Wk LDV and SOF + RBV (N=217)</th><th>24-Wk LDV and SOF (N=217)</th><th>24-Wk LDV and SOF + RBV (N=217)</th></tr>
<tr><td>Efficacy</td><td colspan="4"></td></tr>
<tr><td>SVR12, n (%)</td><td>211 (99)</td><td>211 (97)</td><td>212 (98)</td><td>215 (99)</td></tr>
<tr><td>Safety</td><td colspan="4"></td></tr>
<tr><td>SAE, n (%)</td><td>1 (<1)</td><td>7 (3)</td><td>18 (8)</td><td>7 (3)</td></tr>
<tr><td>Discontinued treatment due to AE, n (%)</td><td>0</td><td>0</td><td>4 (2)</td><td>6 (3)</td></tr>
<tr><td>Any AE, n (%)</td><td>169 (79)</td><td>185 (85)</td><td>178 (82)</td><td>200 (92)</td></tr>
<tr><td>Anemia, n (%)</td><td>0</td><td>25 (12)</td><td>0</td><td>22 (10)</td></tr>
<tr><td>Rash, n (%)</td><td>16 (7)</td><td>21 (10)</td><td>16 (7)</td><td>27 (12)</td></tr>
<tr><td>Depression, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
</table>

Authors' Conclusion:

Once-daily of fixed-dose combination LDV and SOF with or without RBV for 12 or 24 weeks was highly effective in patients with HCV genotype 1 infection who are treatment naïve

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</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Kowdley,[15] 2014, US</td><td>

Main Findings:

Outcome	8-Wk LDV and SOF (N=215)	8-Wk LDV and SOF + RBV (N=216)	12-Wk LDV and SOF (N=216)
Efficacy			
SVR12, n (%)	202 (94)	201 (93)	206 (95)
Safety			
SAE, n (%)	4 (2)	1 (<1)	5 (2)
Discontinued treatment due to AE, n (%)	0	1 (<1)	2 (1)
Any AE, n (%)	145 (67)	165 (76)	149 (69)
Anemia, n (%)	2 (1)	17 (8)	2 (1)
Rash, n (%)	3 (1)	19 (9)	5 (2)
Depression, n (%)	NR	NR	NR

Authors' Conclusion:

Once-daily of fixed-dose combination LDV and SOF for 8 weeks was associated with a high rate of SVR among treatment naïve patients with HCV genotype 1 infection without cirrhosis. The inclusion of ribavirin in the regimen and the extension of the duration of treatment to 12 weeks were not associated with additional benefit.

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<tr><td>Osinusi,[19] 2013, US</td><td>

Main Findings:

Outcome	SOF + Weight-Based RBV (n=10)	SOF + Weight-Based RBV (n=25)	SOF + low dose RBV (n=25)
Efficacy			
SVR24, n (%)	9 (90)	17 (68)	12 (48)
Safety			
SAE, n (%)	NR	0	1 (4)
Discontinued treatment due to AE, n (%)	NR	0	0
Any AE, n (%)	NR	NR	NR
Anemia, n (%)	NR	8 (32)	4 (16)
Rash, n (%)	NR	2 (8)	0
Depression, n (%)	NR	NR	NR

Authors' Conclusion:

In a patient population with a high prevalence of unfavorable traditional predictors of treatment response, SVR24 rates of a 24-week regimen of SOF and weight-based or low-dose RBV were 68% and 48%, respectively

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</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Lawitz,[17] 2014, US</td><td>

Main Findings:

<table>
<tr><th>Outcome</th><th colspan="3">treatment-naive patients</th><th colspan="2">patients previously treated with PI</th></tr>
<tr><td></td><td>8-Wk LDV and SOF (N=20)</td><td>8-Wk LDV and SOF + RBV (N=21)</td><td>12-Wk LDV and SOF (N=19)</td><td>12-Wk LDV and SOF (N=19)</td><td>12-Wk LDV and SOF + RBV (N=21</td></tr>
<tr><td>Efficacy</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SVR12, n (%)</td><td>19 (95)</td><td>21 (100)</td><td>18 (95)</td><td>18 (95)</td><td>21 (100)</td></tr>
<tr><td>SVR24, n (%)</td><td>19 (95)</td><td>21 (100)</td><td>18 (95)</td><td>18 (95)</td><td>21 (100)</td></tr>
<tr><td>Safety</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SAE, n (%)</td><td>0</td><td>1 (5)</td><td>1 (5)</td><td>1 (5)</td><td>1 (5)</td></tr>
<tr><td>Discontinued treatment due to AE, n (%)</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Any AE, n (%)</td><td>9 (45)</td><td>12 (57)</td><td>8 (42)</td><td>7 (37)</td><td>12 (57)</td></tr>
<tr><td>Anemia, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Rash, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Depression, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
</table>

Authors' Conclusion:

Once-daily of fixed-dose combination LDV and SOF with or without RBV has the potential to cure most patients with genotype-1 HCV, regardless of the presence of compensated cirrhosis or treatment history.

</td></tr>
<tr><td>Sulkowski,[18] 2014, US</td><td>

Main Findings:

<table>
<tr><th>Outcome</th><th colspan="5">treatment-naive patients</th><th colspan="2">patients previously treated with PI</th></tr>
<tr><td></td><td>SOF for 7 days, then SOF and DCV for 23-wk (N = 15)</td><td>DCV and SOF for 24-wk (N = 14)</td><td>DCV and SOF plus RBV for 24-wk (N = 15)</td><td>DCV and SOF for 12-wk (N = 41)</td><td>DCV and SOF plus RBV for 12-wk (N = 41)</td><td>DCV and SOF for 24-wk (N = 21)</td><td>DCV and SOF plus RBV for 24-wk (N = 20)</td></tr>
<tr><td>Efficacy</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SVR12, n (%)</td><td>15 (100)</td><td>14 (100)</td><td>15 (100)</td><td>41 (100)</td><td>39 (95)</td><td>21 (100)</td><td>19 (95)</td></tr>
<tr><td>SVR24, n (%)</td><td>14 (93)</td><td>14 (100)</td><td>15 (100)</td><td>39 (95)</td><td>38 (93)</td><td>NR</td><td>NR</td></tr>
<tr><td>Safety</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SAE, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>1 (2)</td><td>0</td><td>0</td><td>1 (5)</td></tr>
<tr><td>Discontinued treatment due to AE, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Any AE, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>38 (93)</td><td>38 (93)</td><td>16 (76)</td><td>20 (100)</td></tr>
<tr><td>Anemia, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Rash, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Depression, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
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<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
Once-daily DCV plus SOF was associated with high rates of SVR among patients infected with HCV genotype 1 including patients with no prior response to therapy with telaprevir or boceprevir.</td></tr>
<tr><td>Gane,[21] 2013, New Zealand</td><td>Main Findings:
<table>
<tr><th>Outcome</th><th>12-Wk SOF + RBV treatment-naive patients (N=25)</th><th>12-Wk SOF + RBV patients previously treated with PR (N=10)</th></tr>
<tr><td>Efficacy</td><td></td><td></td></tr>
<tr><td>SVR12, n (%)</td><td>21 (84)</td><td>1 (10)</td></tr>
<tr><td>SVR24, n (%)</td><td>21 (84)</td><td>1 (10)</td></tr>
<tr><td>Safety</td><td></td><td></td></tr>
<tr><td>SAE, n (%)</td><td>NR</td><td>NR</td></tr>
<tr><td>Discontinued treatment due to AE, n (%)</td><td>0</td><td>0</td></tr>
<tr><td>Any AE, n (%)</td><td>NR</td><td>NR</td></tr>
<tr><td>Anemia, n (%)</td><td>5 (20)</td><td>3 (30)</td></tr>
<tr><td>Rash, n (%)</td><td>4 (16)</td><td>3 (30)</td></tr>
<tr><td>Depression, n (%)</td><td>NR</td><td>NR</td></tr>
</table>
Authors' Conclusion:
Twelve weeks of SOF plus RBV may be effective in patients with HCV genotype 1 infection who are treatment naïve.</td></tr>
<tr><td>Gane,[20] 2014, New Zealand</td><td>Main Findings:
<table>
<tr><th>Outcome</th><th colspan="3">treatment-naive patients</th><th colspan="4">patients previously treated with PR</th></tr>
<tr><td></td><td>12-Wk LDV + SOF + RBV (N=25)</td><td>12 WK SOF + GS-9669 + RBV (N=25)</td><td>6-Wk LDV and SOF + RBV (N=25)</td><td>12-Wk LDV + SOF + RBV (N=9)</td><td>12 Weeks SOF + GS-9669 + RBV (N=10)</td><td>12-Wk LDV and SOF cirrhotic patients (N=10)</td><td>12-Wk LDV and SOF + RBV cirrhotic patients (N=9)</td></tr>
<tr><td>Efficacy</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SVR12, n (%)</td><td>25 (100)</td><td>23 (92)</td><td>17 (68)</td><td>9 (100)</td><td>10 (100)</td><td>7 (70)</td><td>9 (100)</td></tr>
<tr><td>Safety</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SAE, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Discontinued treatment due to AE, n (%)</td><td>1 (4)</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Any AE, n (%)</td><td>24 (96)</td><td>25 (100)</td><td>22 (88)</td><td>9 (100)</td><td>10 (100)</td><td>7 (70)</td><td>8 (89)</td></tr>
<tr><td>Anemia, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Rash, n (%)</td><td>4 (16)</td><td>5 (20)</td><td>3 (12)</td><td>1 (11)</td><td>1 (10)</td><td>0</td><td>0</td></tr>
<tr><td>Depression, n (%)</td><td>4 (16)</td><td>0</td><td>0</td><td>2 (22)</td><td>1 (10)</td><td>0</td><td>1 (11)</td></tr>
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<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
The combination of SOF and a second DAA agent is highly effective in patients with HCV genotype 1 infection who are treatment naïve or did not respond to previous treatment</td></tr>
<tr><td>Afdhal,[16]
2014, US</td><td>Main Findings:
<table><tr><th>Outcome</th><th>12-Wk LDV and SOF (N=109)</th><th>12-Wk LDV and SOF + RBV (N=111)</th><th>24-Wk LDV and SOF (N=109)</th><th>24-Wk LDV and SOF + RBV (N=111)</th></tr><tr><td colspan="5">Efficacy</td></tr><tr><td>SVR12, n (%)</td><td>102 (94)</td><td>107 (96)</td><td>108 (99)</td><td>110 (99)</td></tr><tr><td>SVR24, n (%)</td><td>102 (94)</td><td>107 (96)</td><td>108 (99)</td><td>110 (99)</td></tr><tr><td colspan="5">Safety</td></tr><tr><td>SAE, n (%)</td><td>0</td><td>0</td><td>6 (6)</td><td>3 (3)</td></tr><tr><td>Discontinued treatment due to AE, n (%)</td><td>0</td><td>0</td><td>0</td><td>0</td></tr><tr><td>Any AE, n (%)</td><td>73 (67)</td><td>96 (86)</td><td>88 (81)</td><td>100 (90)</td></tr><tr><td>Anemia, n (%)</td><td>0</td><td>9 (8)</td><td>1 (1)</td><td>12 (11)</td></tr><tr><td>Rash, n (%)</td><td>2 (2)</td><td>11 (10)</td><td>6 (6)</td><td>16 (14)</td></tr><tr><td>Depression, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr></table>Authors' Conclusion:
Once-daily of fixed-dose combination LDV and SOF resulted in high rates of SVR in patients with HCV genotype 1 infection who had not had a SVR to prior interferon based treatment.</td></tr>
<tr><td colspan="2">Economic evaluations</td></tr>
<tr><td>Hagan,[22]
2014, US</td><td>Data from clinical trials of SOF plus SIM or SOF plus RBV were used for efficacy.
Base case results:<table><tr><th>Outcome</th><th>SOF +SMV</th><th>SOF + RBV</th></tr><tr><td>Cost</td><td>$165,336</td><td>$243,586</td></tr><tr><td>QALYs</td><td>14.69</td><td>14.45</td></tr><tr><td>Cost/QALY</td><td>$11,255</td><td>$16,857</td></tr><tr><td>Cost per SVR</td><td>$170,456</td><td>$262,046</td></tr><tr><td>Cost savings per SVR with SOF + SMV</td><td>$91,590</td><td></td></tr></table>Sensitivity analyses:
The variation of different parameters (disease characteristics, SVR rates, tolerability, and retreatment) did not reverse the findings that SIM + SOF is costing less per SVR than SOF + RBV.
Authors' Conclusion:
Results suggest that a 12-week course of SIM + SOF is more cost effective than 24 weeks of SOF + RBV in treatment of patients with chronic HCV genotype 1 infection who are interferon ineligible or intolerant.</td></tr>
<tr><td colspan="2">AE=adverse event; HCV=hepatitis C Virus; DCV=daclatasvir; LDV=Ledipasvir; NR=Not Reported; PI=protease inhibitors; PR=pegylated interferon alfa plus ribavirin; RBV=Ribavirin; SAE=Serious adverse event; SIM=Simeprevir; SOF=Sofosbuvir; SVR12=sustained virological response 12 weeks after the end of treatment; SVR24=sustained virological response 24 weeks after the end of treatment; UK=the United Kingdom; US=the United States of America; Wk=week</td></tr>
</table>

APPENDIX 5: ADDITIONAL REFERENCES OF POTENTIAL INTEREST

ClinicalTrials.gov [Internet]. Bethesda (MD): US National Institute of Health; 2000 Feb 29 -. Identifier NCT01466790, A study of TMC435 in combination with PSI-7977 (GS7977) in chronic Hepatitis C genotype 1-infected prior null responders To Peginterferon/Ribavirin therapy or HCV treatment-naive patients (COSMOS); 2014 Feb 25 [cited 2014 Jun 25]. Available from: http://clinicaltrials.gov/ct2/show/NCT01466790?term=cosmos&rank=5

Lawitz E, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype-1 prior null-responder / treatment-naïve patients (COSMOS study): primary endpoint (SVR12) results in patients with METAVIR F3-4 (Cohort 2) [Internet]. Abstract presented at: EASL - The International Liver Congress. 49th Annual Meeting of the European Association for the Study of the Liver; 2014 Apr 9-13; London (UK). [cited 2014 Jun 25]. Available from: http://www.natap.org/2014/EASL/EASL_26.htm

Sulkowski MS, Jacobson IM, Ghalib R, Rodriguez-Torres M, Younossi Z, et al. Once-daily simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype-1 prior null responders with METAVIR F0-2: COSMOS study subgroup analysis [Internet]. Abstract presented at: EASL - The International Liver Congress. 49th Annual Meeting of the European Association for the Study of the Liver; 2014; Apr 9-13; London (UK). [cited 2014 Jun 25]. Available from: http://www.natap.org/2014/EASL/EASL_46.htm