

AHRQ Comparative Effectiveness Review Surveillance Program

CER #76: Treatment for Hepatitis C Virus Infection in Adults

Original Release Date: November, 2012

Surveillance Report: August, 2015

Summary of Key Findings from Surveillance Report:

- All conclusions for Key Questions 1- 4 are likely still current; however, due to the discontinuation of the marketing and production of Boceprevir and Telaprevir, and the discontinued use of pegylated interferon in the United States, these conclusions are no longer applicable to current practice.
- New interventions for HCV (e.g., Ledipasvir/Sofosbuvir; Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir) have been approved since the publication of the original CER. Information about these treatments were not assessed in this surveillance report.

Signal Assessment: The signals examined in this surveillance assessment suggest that the original CER is out of date.

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Conflict of Interest:

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Introduction

The purpose of the surveillance process for the EPC Program is to determine whether the conclusions of a systematic review are current. The surveillance process examines the conclusions to the key questions as written, and does not evaluate the currency of the original scope (i.e., key questions, included interventions). Approximately 25 systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #76 titled “Treatment for Hepatitis C Virus Infection in Adults” was originally released in November, 2012.¹

The key questions for the original CER are as follows:

Key Question 1.

- 1a What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?
- 1b How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?

Key Question 2.

- 2a What is the comparative effectiveness of antiviral treatments in improving intermediate outcomes, such as the rate of the rate of SVR or histologic changes in the liver?
- 2b How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?

Key Question 3.

- 3a What are the comparative harms associated with antiviral treatment?
- 3b Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers?

Key Question 4. Have improvements in intermediate outcomes (SVR, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?

Our surveillance assessment began in July 2015. We conducted an electronic search for literature published since the end date of the original CER. After completing a scan of this literature to identify evidence potentially related to the key questions in this CER, we contacted experts involved in the original CER to request their opinions as to whether the conclusions had changed.

Methods

Literature Searches

We conducted a literature search of PubMed covering January 2012 to July 2015, using the search strategy reported as updated after peer review in the original report¹ and searching for studies published since the end date of the original CER.

The search was conducted to assess the currency of conclusions. This process included selecting journals from among the top 10 journals from relevant specialty subject areas (Appendix A) and among those most highly represented among the references for the original report (Appendix B). The included journals were six high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Cochrane Database of Systematic Reviews, Journal of the American Medical Association, Lancet, and New England Journal of Medicine), and five specialty journals (Gastroenterology, Hepatology, Journal of Hepatology, Journal of Gastroenterology and Hepatology, and Journal of Viral Hepatitis). The search strategy is reported in Appendix C.

Study Selection

Using the same inclusion and exclusion criteria as the original CER (see Appendix D), one investigator reviewed the titles and abstracts of the 11 high-impact journal search results (Appendix E).

Expert Opinion

We shared the conclusions of the original report and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with eleven experts in the field (original peer reviewers, technical expert panel members [TEP], and a local expert) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Three subject matter experts responded to our request. Appendix F shows the form experts were asked to complete.

Horizon Scanning

The AHRQ Healthcare Horizon Scanning System identifies emerging health care technologies and innovations with the potential to impact health care for AHRQ's 14 priority conditions.⁴ We reviewed the Infectious Disease Including HIV/AIDS section to identify new potentially high-impact interventions related to the key questions in this CER. Potentially high impact interventions were considered in the final assessment of the currency of the report and its conclusions.

FDA Black Box Warnings

We searched the FDA MedWatch online database website for black box warnings relevant to the key questions in this CER.

Check for Qualitative Signals

The authors of the original CER conducted qualitative and quantitative synthesis of data on the comparative effectiveness and harms associated with antiviral treatment for HCV, and a qualitative analysis of the data examining the reduction of the risks and adverse events due to improvements in intermediate outcomes such as histologic changes in the liver. We compared the conclusions of the included abstracts to the conclusions of the original CER, and assessed expert opinions to identify qualitative signals about the currency of conclusions.

Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix G) that includes the key questions and conclusions from the original CER, findings of the new literature search, FDA Black box warnings, and the expert assessments that pertained to each key question. We categorized the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the CER is likely current
- Original conclusion is possibly out of date and this portion of the CER may not be current
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as likely current.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly not current.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

Signal Assessment for Currency of the CER

We used the following considerations in our assessment of currency of the CER:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original report out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal when new evidence is identified which may change the conclusions from the original report. This may occur when abstract review and expert assessment indicates that some conclusions from the original report may not be current, or when it is unclear from abstract review how new evidence may impact the findings from the original report. In this case, full-text review and data abstraction may be needed to more clearly classify a signal.
- **Weak signal:** A report is considered to have a weak signal if little or no new evidence is identified that would change the conclusions from the original report. This may occur when little to no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original report.

Results

Literature Search

The literature search identified 12 unique titles from the 11 selected high profile general medical and specialty journals (Appendix E). Upon abstract review, 11 studies were rejected because they did not

meet the original CER inclusion criteria (see Appendix D). The remaining one study² was examined for potential to change the results of the original review.

Horizon Scanning

We identified four interventions, *Daclatasvir (Daklinza) for treatment of chronic hepatitis C virus infection*, *Ledipasvir and sofosbuvir (Harvoni) for treatment of chronic hepatitis C virus infection*, *Ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets (Viekira Pak) for treatment of chronic hepatitis C virus infection*, and *Sofosbuvir (Sovaldi) for treatment of chronic hepatitis C virus infection*. The high impact potential for these interventions are on the high end of the high-impact-potential range, and are closely related to the key questions for this CER.

FDA Black Box Warnings

We found one relevant black box warning: Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."

Expert Opinion

We shared the conclusions of the original report with eleven experts in the field (original peer reviewers, TEP members) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Three subject matter experts responded.

Three experts identified potentially one potentially relevant study for Key Question 1³. The reviewers agreed that the conclusions for Key Questions 1-4 were still current. However, two reviewers noted that studies of new HCV medications had not been identified in the 2015 literature search, that Telaprevir and Boceprevir are no longer marketed, and that pegylated interferon is not being used in the U.S. See Appendix G for more detail.

Identifying Qualitative Signals

Appendix G shows the original key questions, the conclusions of the original report, the results of the literature search, FDA black box warnings, the experts' assessments, and the conclusions regarding the currency of the CER.

We identified no new studies for Key Questions 1. We identified one study² for Key Question 2, which compared dual therapy PEG-IFN alfa-2b plus Ribavirin to two doses of a new vaccine TG4040 as part of PEG-IFN alfa-2b plus Ribavirin triple therapy on sustained virologic response. Results indicated better sustained virologic response associated with the study drug. In addition, related to Key Question 3, one study³, identified through peer review, compared PEG-IFN alfa-2a to PEG-IFN alfa-2b with ribavirin for 24 or 48 weeks in Korea, and found that unlike the Western data, efficacy and safety of PEG-IFN alfa-2a were similar to those of PEG-IFN alfa-2b in chronically HCV-infected Korean patients regardless of age, HCV viral load, and hepatic fibrosis. No new studies were identified for Key Question 4, and neither of the identified studies for Key Questions 2 or 3 had the potential to change the conclusions of the original CER.

Since the original CER was published, two direct acting antivirals have been discontinued by their manufacturers due to a reduction in demand, with both Boceprevir⁴ and Telaprevir available only through December 2015. In addition, prior to discontinuation (2014), the FDA added a boxed warning to

Telaprevir for adverse events related to potentially fatal skin reactions⁵. Furthermore, pegylated interferon is no longer being used in the United States.

The conclusions of the original CER relate directly to the comparative effectiveness of various combinations of pegylated interferon with or without Teleprevir or Boceprevir. While these conclusions remain valid, the discontinuation of these drugs render them out of date.

Finally, since the publication of the original CER, new interventions for HCV, such as those identified by our Horizon Scan (e.g., Ledipasvir/Sofosbuvir; Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir) have been approved.⁶ Information about these treatments were not assessed in this surveillance report.

Signal Assessment

The SRC conclusions based on the results of literature published since the original report, FDA boxed warnings, horizon scanning, and expert assessment is that:

- All conclusions for Key Questions 1- 4 are out of date due to the discontinuation of the marketing and production of Boceprevir and Telaprevir, and the discontinued use of pegylated in the United States.

The signal for this report is strong, suggesting that the conclusions in the original CER are out of date.

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Appendices

Appendix A: Top 10 Journals

Appendix B: Most Cited Journals from Original Systematic Review

Appendix C: Original Search Strategy

Appendix D: Inclusion and Exclusion Criteria from Original Systematic Review

Appendix E: Literature Search Results

Appendix F: Questionnaire Sent to Expert Reviewers

Appendix G: Summary Table

Appendix A. Top 10 Journals

In the Journal Citation Reports database, the science and social science sections were searched by subject area discipline(s) for each surveillance reports topic area. For each subject area discipline, the list was constructed by selecting the top 10 journals from the 5 year citation impact factor average list. Selected citations were downloaded in .csv format.

Infectious Disease:

1. Lancet Infectious Disease
2. Clinical Infectious Diseases
3. Emerging Infectious Diseases
4. Journal of Infectious Diseases
5. AIDS
6. Clinical Microbiology and Infection
7. Journal of Antimicrobial Chemotherapy
8. Journal of the International AIDS Society
9. Journal of Acquired Immune Deficiency Syndromes
10. Infectious Control Hospital Epidemiology

Top 10 General Medical:

1. Annals of Internal Medicine
2. Archives of Internal Medicine
3. BMC Medicine
4. The BMJ
5. Journal of Cachexia, Sarcopenia and Muscle
6. JAMA Internal Medicine
7. JAMA
8. Lancet
9. New England Journal of Medicine
10. PLOS Medicine

Appendix B. Most Cited Journals from Original Systematic Review

Rank	Journal	# of Citations
1	Hepatology	20
2	Gastroenterology	12
3	Journal of Viral Hepatitis	9
4	New England Journal of Medicine	8
5	Journal of Hepatology	6
6	Journal of Gastroenterology & Hepatology	5
7	American Journal of Gastroenterology	4
8	Annals of Internal Medicine	3
9	Antiviral Therapy	2
9	Gut	2
9	Intervirolgy	2
9	Lancet	2
9	Liver International	2

Appendix C. Original Search Strategy

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to June Week 4 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 06, 2015>	
Search Strategy:	
<p>1 Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus\$.mp. or HCV.mp. (74601)</p> <p>2 Antiviral agents/ or Interferons/ or Interferon-alpha/ or Interferon Alfa-2a/ or Interferon Alpha-2b/ or Interferon\$.mp. or interferon alpha-2a.mp. or interferon alpha-2b.mp. or IFNalpha2a.mp. or IFNalpha2b.mp. or interferon alpha 2a.mp. or interferon alpha 2b.mp. or exp Polyethylene Glycols/ or pegasys.mp. or Peg-intron.mp. or peginterferon alpha-2a.mp. or peginterferon alpha-2b.mp. or peginterferon alpha 2a.mp. or peginterferon alpha 2b.mp. or pegylated interferon\$.mp. or IFN\$.mp. or PEG IFN\$.mp. or Ribavirin/ or ribavirin.mp. or RBV.mp. or exp Protease Inhibitors/ or protease inhibitor\$.mp. or polymerase inhibit\$.mp. or HCV protease\$.mp. or telaprevir.mp. or boceprevir.mp. (465162)</p> <p>3 1 and 2 (24072)</p> <p>4 (randomized controlled trial or controlled clinical trial or meta analysis or review).pt. or clinical trials as topic/ or cohort studies/ or randomized.ab. or randomly.ab. or placebo.ab. or (systematic adj1 review).ti.ab. (3014756)</p> <p>5 3 and 4 (7753)</p> <p>6 limit 5 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)")) (2084)</p> <p>7 (unsafe or safety or harm\$ or complication\$ or poison\$ or risk\$.mp. or AE.fs. or MO.fs. or PO.fs. or TO.fs. or CT.fs. or side-effect\$.mp. or (undesirable adj1 effect\$.mp. or (treatment adj1 emergent).mp. or tolerab\$.mp. or toxic\$.mp. or adrs.mp. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp. (4836846)</p> <p>8 1 and 2 and 7 (10259)</p> <p>9 4 and 8 (4375)</p> <p>10 limit 9 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)")) (1348)</p> <p>11 Counseling/ or Sex Counseling/ or Health Education/ or Patient Education as Topic/ or Psychotherapy/ or Behavior Therapy/ or Cognitive Therapy/ or Immunization/ or Immunotherapy/ or Psychotherapy, Brief/ or Socioenvironmental Therapy/ (300280)</p> <p>12 1 and 11 (820)</p>	Original Updated Search after Peer Review
13 "annals of internal medicine".jn. (30458)	Journal Limits : general medicine

14	bmj.jn. (62902)	
15	"cochrane database of systematic reviews".jn. (11505)	
16	jama.jn. (66896)	
17	lancet.jn. (130265)	
18	"new england journal of medicine".jn. (72471)	
19	gastroenterology.jn. (27677)	Journal Limits : specialty journals
20	hepatology.jn. (14981)	
21	"journal of hepatology".jn. (9202)	
22	"journal of gastroenterology & hepatology".jn. (7650)	
23	"journal of viral hepatitis".jn. (2159)	
24	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (436166)	
25	12 and 24 (61)	
26	limit 25 to yr="2012 -Current" (13)	Date Limits

Appendix D. Inclusion and Exclusion Criteria from Original Systematic Review

Populations	<p>Asymptomatic adults with chronic hepatitis C virus infection who have not received antiviral drug treatment previously</p> <p>Subgroups include: HCV genotype, race, sex, stage of disease, viral load, weight, and others (e.g. genetic markers)</p> <ul style="list-style-type: none"> Excluded: Pregnant women, HIV co-infected, transplant recipients, patients with renal failure
Interventions	<p>KQ 1a and b:</p> <p>1c 1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?</p> <p>1d 1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 2a and b:</p> <p>What is the comparative effectiveness of antiviral treatments in improving intermediate outcomes, such as the rate of viremia, aminotransaminase levels, and histologic changes?</p> <p>2a How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 3a and b:</p> <p>3c What are the comparative harms (including intolerance to treatment) associated with antiviral treatment?</p> <p>3d Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 4:</p> <p>Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?</p>
Comparisons	<p>KQ 1a and b:</p> <p>1a What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?</p> <p>1b How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 2a and b:</p> <p>2a What is the comparative effectiveness of antiviral treatments in improving</p>

	<p>intermediate outcomes, such as the rate of viremia, aminotransaminase levels, and histologic changes?</p> <p>2b How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers? KQ 3a and b: 3. What are the comparative harms (including intolerance to treatment) associated with antiviral treatment?</p> <p>3a. Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 4: Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?</p>
Outcomes	<p>Clinical outcomes</p> <ul style="list-style-type: none"> • Mortality (all-cause or hepatic) • Cirrhosis • Hepatic decompensation • Hepatocellular carcinoma • Need for liver transplantation • Quality of life • Harms from antiviral treatments (including withdrawals due to adverse events, neutropenia, anemia, psychological adverse events, flu-like symptoms, rash) <p>Intermediate outcomes</p> <ul style="list-style-type: none"> • Sustained virological response • Improvement in liver histology
Settings	All settings (including primary care and specialty settings) and locales, though focus on studies conducted in the U.S. and other developed countries.
Study Design	<p>KQ 3a and b:</p> <p>3a What are the comparative harms (including intolerance to treatment) associated with antiviral treatment?</p> <p>3b Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 4: Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?</p>

Appendix E. Literature Search Results

1. Akazawa DM, Moriyama M, Yokokawa H, Omi N, Watanabe N, Date T, Morikawa K, Aizaki H, Ishii K, Kato T, Mochizuki H, Nakamura N, Wakita, T. (2013). Neutralizing antibodies induced by cell culture-derived hepatitis C virus protect against infection in mice. *Gastroenterology*,145;2:447-55.e1-4.
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Appendix F. Questionnaire Sent to Expert Reviewers

AHRQ Comparative Effectiveness Review Surveillance Program

Reviewer Form

Title of Original Review: TBD

[Link to Report](#)

Name of Reviewer: _____

Instructions:

The AHRQ Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ reviews to assist with prioritization of reports for updating. One part of this process includes soliciting expert review of our synthesis of recently published literature and FDA black box warnings.

The attached document includes a table highlighting the conclusions from the original report and our synthesis of the recently published literature. Abstracts from relevant literature are included at the end of the attached document. If you would like a list of our full search results, please let us know.

Please review the table in the attached document and provide responses to the questions for each key question below. The primary goal of this review is to identify any missing studies and ensure the accuracy of our synthesis of the recently published literature.

Key Question 1a:

What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?

Long-term clinical outcomes

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Short-term mortality

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Short-term quality of life

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 1b:

How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 2a:

What is the comparative effectiveness of antiviral treatments on intermediate outcomes?

Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Duration Effects

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Dose Effects

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir: Dose effects of Pegylated Interferon Alfa-2a vs. Alfa-2b and Duration effects

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Other

SRC Literature Analysis:

- One study found that a higher percentage of patients who received immunotherapy with TG4040 followed by TG4040 and PEG-IFN α /RBV achieved a cEVR compared with patients who received only PEG-IFN α /RBV therapy

Reviewer Questions:

3. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

4. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 2b:

How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?

Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 3:

Do these harms differ according to patient subgroup characteristics?

Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir or Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 4:

Have improvements in intermediate outcomes been shown to reduce risk or rates of adverse health outcomes from HCV infection?

Mortality and long-term hepatic complications

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Short-term quality of life

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Title of Original Review: TBD

[Link to Report](#)

The conclusions from the original report and an analysis of recent literature identified by the Scientific Resource Center (SRC) are summarized below. Abstracts are provided for included literature at the end of the document.

Conclusions From Original Review, SOE = Strength of Evidence	SRC Literature Analysis
Key Question 1a: What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?	
Long-term clinical outcomes SOE: Insufficient No evidence.	No new research was found
Short-term mortality SOE: Low 3 trials compared current antiviral regimens ¹ , but found no difference in short-term mortality. Very few (20 total) events reported.	No new research was found
Short-term quality of life SOE: Low Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. pegylated interferon alfa-2b plus ribavirin (1 open-label randomized trial) found slightly better short-term scores favoring pegylated interferon alfa-2a plus ribavirin for patients with genotype-4 infection.	No new research was found
Key Question 1b: How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?	
Any clinical outcome SOE: Insufficient No evidence.	No new research was found
Key Question 2a: What is the comparative effectiveness of antiviral treatments on intermediate outcomes?	
Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin Outcome: Sustained virologic response SOE: Moderate 7 trials found pegylated interferon alfa-2b plus ribavirin to be associated with lower likelihood of achieving an SVR (pooled RR 0.87, 95% CI: 0.80 to 0.95; I ₂ =27.4%)	No new research was found

<ul style="list-style-type: none"> Absolute difference in SVR rates: 8% (95% CI: 3 to 14) 	
<p>Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Duration Effects</p> <p>Outcome: Sustained virologic response</p> <p>SOE: Moderate</p> <p>48 vs. 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin:</p> <ul style="list-style-type: none"> 2 trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving SVR (pooled RR 0.97, 95% CI: 0.84 to 1.1; I₂=43%) <p>24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b):</p> <ul style="list-style-type: none"> 4 trials of patients with genotype 2 or 3 infection favored 24 weeks of therapy more effective for achieving SVR (pooled RR 1.15; 95% CI: 1.02 to 1.29; I₂=79.5%) Relative risk estimates: 1.01 to 1.33; may vary due to differences across studies in ribavirin dosing. <p>24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin:</p> <ul style="list-style-type: none"> 3 trials of patients with genotype 2 or 3 infection with a rapid virologic response (undetectable HCV-RNA by week 4) found no differences (RR 0.99, 95% CI: 0.86 to 1.14; I₂=66.7%). Relative risk estimates: 0.89 to 1.2. 	<p>No new research was found</p>
<p>Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Dose Effects</p> <p>Outcome: Sustained virologic response</p> <p>SOE: Moderate</p> <p>Low (0.75-1.0 mcg/kg or 50 mcg) vs. high doses (1.5 mcg/kg or 100-150 mcg) of pegylated interferon alfa-2b :</p> <ul style="list-style-type: none"> 6 trials found lower doses associated with lower likelihood of achieving SVR for patients with genotype 2 or 3 infection (Pooled RR 0.90; 95% CI: 0.81 to 0.99; I₂=20.2%) <p>Low (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) vs. high doses (800 or 1,200 mg flat dose or 800 to 1,400 mg weight-based dose) of ribavirin:</p> <ul style="list-style-type: none"> 3 trials of patients with genotype 2 or 3 infection who did not specifically have 	<p>No new research was found</p>

<p>advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR.</p> <p>SOE: Low</p> <p>48 weeks of triple therapy with boceprevir using a low dose of ribavirin (400-1,000 mg daily) vs. 48 weeks of triple therapy with a standard ribavirin dose (800-1,400 mg daily):</p> <ul style="list-style-type: none"> 1 trial of patients with genotype 1 infection found 48 weeks of triple therapy with boceprevir using a low dose of ribavirin to be associated with a non-statistically significant trend toward lower likelihood of SVR (36% vs. 50%, RR 0.71, 95% CI 0.39 to 1.3) 	
<p>Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin</p> <p>Outcome: Sustained virologic response</p> <p>SOE: Moderate</p> <p>Triple therapy with telaprevir for 24 weeks (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> 3 trials of patients with genotype 1 infection found triple therapy with telaprevir to be associated with a higher likelihood of SVR (pooled RR 1.48, 95% CI: 1.26 to 1.75; I₂=0.0%) Absolute increase in SVR rate: 22% (95% CI 13 to 31). <p>Triple therapy with pegylated interferon, ribavirin, and telaprevir for 12 weeks vs. . dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> 1 trial of patients with genotype 1 infection found no difference in likelihood of SVR <p>SOE: Low</p> <p>Response guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by a response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin for an additional 12 or 36 weeks) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> 1 trial of patients with genotype 1 infection found response guided triple therapy with telaprevir to be associated with higher likelihood of SVR. Absolute increase in SVR rate: 25% to 31% 	<p>No new research was found</p>

<p>8 week telaprevir vs. 12 week teleprevir regimen:</p> <ul style="list-style-type: none"> 8 week regimen associated with a slightly lower SVR rate (69% vs. 75%) <p>Triple therapy with telaprevir for 48 weeks (12 weeks of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 36 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin) vs. triple therapy with telaprevir for 24 weeks (12 weeks of triple therapy followed by 12 weeks of dual therapy).</p> <ul style="list-style-type: none"> 1 trial of patients with genotype 1 found no difference in likelihood of SVR. 	
<p>Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir: Dose effects of Pegylated Interferon Alfa-2a vs. Alfa-2b and Duration effects</p> <p>Outcome: Sustained virologic response</p> <p>SOE: Low</p> <p>1 trial of response-guided triple therapy with telaprevir (24 or 48 weeks, based on absence or presence of HCV-RNA from weeks 4 through 20) found similar SVR rates (81–85%) for regimens that varied on telaprevir dose (750 mg tid vs. 1,125 mg bid) and type of pegylated interferon (alfa-2a or alfa-2b).</p> <p>1 trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92% and 88%) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy.</p>	<p>No new research was found</p>
<p>Not in original CER</p>	<p>One RCT examined the new vaccine TG4040 and compared dual therapy with PEG-IFNα/RBV for 48 weeks (Group A) to triple therapy with PEG-IFNα/RBV for 4 weeks followed by PEG-IFNα/RBV for 44 weeks with 6 injections of TG4040 (Group B) to triple therapy with TG4040 for 12 weeks (7 injections) followed by PEG-IFNα/RBV for 48 weeks with 6 injections of TG4040 (Group C). Findings indicated that after 24 weeks, A higher percentage of patients achieved a</p>

	sustained virologic response 24 weeks after therapy ended in group C (58.2%) than in groups A (48.4%) or B (50.8%)
Key Question 2b: How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?	
<p>Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin Outcome: Sustained virologic response SOE: Low</p> <p>Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin:</p> <ul style="list-style-type: none"> • Largest trial (N=3,070) found no clear differences in relative risk estimates for SVR in genotype 1 patients stratified by race, sex, age, baseline fibrosis stage, or baseline viral load. • Characteristics associated with lower absolute SVR rates: <ul style="list-style-type: none"> ○ Older age ○ Black race ○ Advanced fibrosis or cirrhosis ○ High baseline viral load <p>SOE: Moderate</p> <p>Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin:</p> <ul style="list-style-type: none"> • 4 trials found no clear differences in relative risk estimates for SVR in patients stratified by genotype. • Genotype 1 infection was associated with lower absolute SVR rate than genotypes 2 and 3. 	No new research was found
<p>Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin Outcome: Sustained virologic response SOE: Moderate</p> <p>Triple therapy with boceprevir for 48 weeks (4 weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by 44 weeks of triple therapy with pegylated interferon,</p>	No new research was found

<p>ribavirin, and boceprevir) (2 trials):</p> <ul style="list-style-type: none"> • Men vs. Women: No difference in relative risk estimates for SVR • Blacks vs. Non-Black patients: No clear difference in relative risk estimates. Black race associated with lower SVR. <p>Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin:</p> <ul style="list-style-type: none"> • 2 trials found triple therapy to be associated with a higher likelihood of achieving SVR in patients with high baseline HCVRNA viral load (>600,000 or 800,000 IU/mL). Found no difference in likelihood of SVR in patients of lower viral load. 	
<p>Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin</p> <p>Outcome: Sustained virologic response</p> <p>SOE: Moderate (for age and sex); Low (for other factors)</p> <p>Response-guided triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided dual therapy with pegylated interferon alfa-2a and ribavirin) vs. dual therapy with pegylated interferon plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> • 1 trial found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or BMI. • Characteristics associated with lower absolute SVR rates: <ul style="list-style-type: none"> ○ Older age ○ Black race ○ Advanced fibrosis or cirrhosis ○ Higher BMI <p>24-week fixed duration triple therapy with telaprevir, pegylated interferon alfa-2b, and ribavirin vs. 48 weeks of dual therapy:</p> <ul style="list-style-type: none"> • 1 trial found no differences in estimates of effect in patients stratified by sex or age. <p>SOE: Insufficient</p> <p>Triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and telaprevir vs. dual therapy:</p> <p>2 trials reported inconsistent findings for differential relative risk estimates according to baseline</p>	<p>No new research was found</p>

viral load.	
<p>Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin</p> <p>Outcome: Harms</p> <p>SOE: Moderate</p> <p>Dual therapy with pegylated interferon alfa-2b vs. dual therapy with pegylated interferon alfa-2a plus ribavirin:</p> <ul style="list-style-type: none"> • Dual therapy with pegylated interferon alfa-2b was associated with: <ul style="list-style-type: none"> ○ Slightly greater risk of headache (3 trials), pooled RR 1.1, 95% CI 1.1 to 1.2; I2=0%) ○ Lower risk of serious adverse events (2 trials), pooled RR 0.76; 95% CI 0.71 to 0.88; I2=0%) ○ Lower risk of neutropenia (5 trials), pooled RR 0.61, 95% CI 0.46 to 0.83; I2=38% ○ Lower risk of rash (2 trials), pooled RR 0.79, 95% CI 0.71 to 0.88; I2=0.0%). • Found no difference in withdrawals due to adverse events. 	No new research was found
<p>Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin</p> <p>Outcome: Harms</p> <p>SOE: Moderate</p> <p>Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) vs. dual therapy with pegylated interferon alfa-2b plus ribavirin:</p> <ul style="list-style-type: none"> • Triple therapy with boceprevir was associated with: <ul style="list-style-type: none"> ○ Increased risk of neutropenia (2 trials), pooled RR 1.8, 95% CI 1.5 to 2.3; I2=0.0% ○ Dysgeusia (2 trials), pooled RR 2.5, 95% CI 2.0 to 3.2; I2=0.0% ○ Anemia (2 trials), pooled RR 2.0, 95% CI 1.4 to 2.8; I2=0.0% ○ Thrombocytopenia (2 trials), pooled RR 3.2, 95% CI 1.2 to 8.2; I2=0.0% • % Incidence in triple therapy: <ul style="list-style-type: none"> ○ Anemia: 25% ○ Neutropenia: 33% ○ Severe anemia: 4-5% ○ Severe neutropenia: 8-15% 	No new research was found

<p>Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin</p> <p>Outcome: Harms</p> <p>SOE: Moderate</p> <p>12-week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2a plus ribavirin:</p> <ul style="list-style-type: none"> • 2 trials found no statistically significant difference in risk of any assessed adverse event. <p>24-week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon alfa-2a plus ribavirin for 12 weeks) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> • 3 trials found triple therapy to be associated with: <ul style="list-style-type: none"> ○ Increased risk of anemia (3 trials), pooled RR 1.3, 95% CI 1.1 to 1.5; I2=0.0% ○ Rash (3 trials), pooled RR 1.4, 95% CI 1.1 to 1.7, I2=0.0% • Patients randomized to the telaprevir therapy experienced: <ul style="list-style-type: none"> ○ Rash (1 to 2/3 of entire group) ○ Anemia: 27-91% ○ Severe rash: 7-10% ○ Severe anemia: 4-11% • No difference in risk of withdrawal due to adverse events. <p>SOE: Low</p> <p>Response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided duration pegylated interferon alfa-2a and ribavirin) vs. therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> • 1 trial found association between triple therapy and: <ul style="list-style-type: none"> ○ Increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI 2.6 to 5.7) ○ Anemia(38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5) ○ Any rash (36% vs. 24%, RR 1.5, 95% CI 1.2 to 1.8) ○ Severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13) 	<p>No new research was found</p>
<p>Key Question 3: Do these harms differ according to patient subgroup characteristics?</p>	

<p>Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin</p> <p>Outcome: Harms SOE: Insufficient</p> <p>Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin:</p> <ul style="list-style-type: none"> • No trials reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. • 3 trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials. 	<p>No new research was found</p>
<p>Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir or Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin</p> <p>Outcome: Harms SOE: Insufficient</p> <p>Triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir vs. dual therapy with pegylated interferon plus ribavirin:</p> <ul style="list-style-type: none"> • No trial evaluated harms in patient subgroups. • All trials evaluated patients with genotype 1 infection 	
<p>Key Question 4: Have improvements in intermediate outcomes been shown to reduce the risk or rates of adverse health outcomes from HCV infection?</p>	
<p>Outcome: Mortality and long-term hepatic complications SOE: Moderate</p> <p>SVR after antiviral therapy vs. no SVR:</p> <ul style="list-style-type: none"> • 1 large VA hospital study found SVR after antiviral therapy to be associated with lower risk of all-cause mortality (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively). • 18 cohort studies found SVR to be associated with decreased risk of all-cause mortality, liver-related mortality, HCC, and other complications of ESLD • Studies had methodological shortcomings, including inadequate handling of confounders. 10 were conducted in Asia. 	<p>No new research was found</p>
<p>Outcome: Short-term quality of life SOE: Low</p>	<p>No new research was found</p>

SVR vs. no SVR:

- 9 studies found SVR to be associated with greater improvement in measures related to QoL (generic or disease-specific) 24 weeks after the end of antiviral treatment.
 - Differences averaging 5 to 10 points on various SF-36 domains.
- All studies were poor-quality and were characterized by failure to adjust for confounders, high loss to follow-up, and failure to blind patients to SVR status.

Legend: HCV = hepatitis c virus infection; SVR = sustained virologic response; RR = relative risk; HCV-RNA = hepatitis c virus-ribonucleic acid; BMI = body mass index; ESLD = end-stage liver disease; QoL = quality of life

¹ “Current antiviral treatment regimen” refers to dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin, or triple therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin and boceprevir or telaprevir.

Abstract from Relevant Literature

Di Bisceglie et al. 2014

Efficacy of immunotherapy with TG4040, peg-interferon, and ribavirin in a Phase 2 study of patients with chronic HCV infection, Gastroenterology

BACKGROUND & AIMS: TG4040 is a modified vaccinia Ankara (MVA) virus that expresses the hepatitis C virus (HCV) proteins NS3, NS4, and NS5B. We performed a phase II open-label study to determine the efficacy, safety, and immunotherapeutic properties of TG4040 in combination with pegylated interferon alpha-2a and ribavirin (PEG-IFNalpha/RBV) in patients with chronic HCV infection.;**METHODS:**

Treatment-naive patients with HCV genotype 1 infection were assigned randomly to 1 of the following groups: PEG-IFNalpha/RBV for 48 weeks (group A, n = 31), PEG-IFNalpha/RBV for 4 weeks followed by PEG-IFNalpha/RBV for 44 weeks with 6 injections of TG4040 (group B, n = 63), or TG4040 for 12 weeks (7 injections) followed by PEG-IFNalpha/RBV for 48 weeks with 6 injections of TG4040 (group C, n = 59). The primary end point was complete early virologic response (cEVR), defined as HCV-RNA level less than 10 IU/mL after 12 weeks of PEG-IFNalpha/RBV treatment.;**RESULTS:** In group C, 64.2% of evaluable patients achieved cEVR, compared with 30.0% in group A and 45.9% in group B (P = .0003 for group C vs A). A higher percentage of patients achieved a sustained virologic response 24 weeks after therapy ended in group C (58.2%) than in groups A (48.4%) or B (50.8%). HCV- and MVA-specific T-cell responses were observed predominantly in group C. As expected, most patients given injections of TG4040 developed anti-MVA antibodies. The combination of TG4040 and PEG-IFNalpha/RBV was reasonably well tolerated. However, PEG-IFNalpha-associated thrombocytopenia developed in 3 patients who carried the class II HLA allele DRB1*04.;**CONCLUSIONS:** A higher percentage of patients with chronic HCV infection who received immunotherapy with TG4040 followed by TG4040 and PEG-IFNalpha/RBV achieved a cEVR compared with patients who received only PEG-IFNalpha/RBV therapy. These findings show that immunotherapies that activate T cells are effective in patients with chronic HCV infection. ClinicalTrials.gov number, NCT01055821.

Appendix G. Summary Table

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
Key Question 1a: What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?				
<p>Long-term clinical outcomes SOE: Insufficient</p> <p>No evidence.</p>	<p>No new research was identified.</p>	<p>Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. However, two reviewers noted that new HCV medications had not been addressed in the 2015 literature search, and that Telaprevir and Boceprevir are no longer marketed, and that pegylated interferon is not being used in the U.S.</p> <p>One reviewer recommended five articles. Of these articles, none met inclusion criteria. One articles was a case study¹ examining the duration of surveillance, another was a study examining predictive models of clinical outcomes², one examined biomarkers up to 24 weeks³, another study examined long term outcomes associated with pegylated interferon alpha and ribavirin therapy⁴, and the final</p>	<p>Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
			was a review that that did not compare the effectiveness of long term outcomes. ⁵	
<p>Short-term mortality SOE: Low</p> <p>3 trials compared current antiviral regimens¹, but found no difference in short-term mortality. Very few (20 total) events reported.</p>	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."	All three reviewers agreed that the conclusions in the original CER were current. However, two reviewers noted that new HCV medications had not been addressed in the 2015 literature search, and that Telaprevir and Boceprevir are no longer marketed, and that pegylated interferon is not being used in the U.S.	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.
<p>Short-term quality of life SOE: Low</p> <p>Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. pegylated interferon alfa-2b plus ribavirin (1 open-label randomized trial) found slightly better short-term scores favoring pegylated interferon alfa-2a plus ribavirin for patients with genotype-4 infection.</p>	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."	Two of the three reviewers agreed that the conclusions in the original CER were current. One reviewer noted that there is markedly new evidence regarding quality of life associated with new direct acting antivirals. Two studies were provided; however, were not comparative effectiveness studies, thus did not meet inclusion criteria. ^{6,7}	Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
			However, two reviewers noted that new HCV medications had not been addressed in the 2015 literature search, and that Telaprevir and Boceprevir are no longer marketed, and that pegylated interferon is not being used in the U.S.	
Key Question 1b: How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?				
Any clinical outcome SOE: Insufficient No evidence.	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."	All three reviewers agreed that the conclusions in the original CER were current. However, two reviewers noted that new HCV medications had not been addressed in the 2015 literature search, and that Telaprevir and Boceprevir are no longer marketed, and that pegylated interferon is not being used in the U.S.	Original conclusion is still valid and this portion of the CER is likely current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.
Key Question 2a: What is the comparative effectiveness of antiviral treatments on intermediate outcomes?				
Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin Outcome: Sustained virologic response SOE: Moderate	No new research was identified.	None identified	All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer	Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>7 trials found pegylated interferon alfa-2b plus ribavirin to be associated with lower likelihood of achieving an SVR (pooled RR 0.87, 95% CI: 0.80 to 0.95; I₂=27.4%)</p> <ul style="list-style-type: none"> Absolute difference in SVR rates: 8% (95% CI: 3 to 14) 			being used in the U.S.	used in the U.S., this conclusion is not applicable to current practice.
<p>Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Duration Effects Outcome: Sustained virologic response SOE: Moderate</p> <p>48 vs. 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin:</p> <ul style="list-style-type: none"> 2 trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving SVR (pooled RR 0.97, 95% CI: 0.84 to 1.1; I₂=43%) <p>24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b):</p> <ul style="list-style-type: none"> 4 trials of patients with genotype 2 or 3 infection favored 24 weeks of therapy more effective for achieving SVR (pooled RR 1.15; 95% CI: 1.02 to 1.29; I₂=79.5%) Relative risk estimates: 1.01 to 1.33; may vary due to differences across studies in ribavirin dosing. <p>24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin:</p> <ul style="list-style-type: none"> 3 trials of patients with genotype 	No new research was identified.	None identified	All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.	Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>2 or 3 infection with a rapid virologic response (undetectable HCV-RNA by week 4) found no differences (RR 0.99, 95% CI: 0.86 to 1.14; I₂=66.7%).</p> <ul style="list-style-type: none"> Relative risk estimates: 0.89 to 1.2. 				
<p>Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Dose Effects Outcome: Sustained virologic response SOE: Moderate</p> <p>Low (0.75-1.0 mcg/kg or 50 mcg) vs. high doses (1.5 mcg/kg or 100-150 mcg) of pegylated interferon alfa-2b :</p> <ul style="list-style-type: none"> 6 trials found lower doses associated with lower likelihood of achieving SVR for patients with genotype 2 or 3 infection (Pooled RR 0.90; 95% CI: 0.81 to 0.99; I₂=20.2%) <p>Low (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) vs. high doses (800 or 1,200 mg flat dose or 800 to 1,400 mg weight-based dose) of ribavirin:</p> <ul style="list-style-type: none"> 3 trials of patients with genotype 2 or 3 infection who did not specifically have advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR. 	<p>No new research was identified.</p>	<p>None identified</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p>	<p>Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>SOE: Low</p> <p>48 weeks of triple therapy with boceprevir using a low dose of ribavirin (400-1,000 mg daily) vs. 48 weeks of triple therapy with a standard ribavirin dose (800-1,400 mg daily):</p> <ul style="list-style-type: none"> 1 trial of patients with genotype 1 infection found 48 weeks of triple therapy with boceprevir using a low dose of ribavirin to be associated with a non-statistically significant trend toward lower likelihood of SVR (36% vs. 50%, RR 0.71, 95% CI 0.39 to 1.3) 				
<p>Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin</p> <p>Outcome: Sustained virologic response</p> <p>SOE: Moderate</p> <p>Triple therapy with telaprevir for 24 weeks (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> 3 trials of patients with genotype 	<p>No new research was identified.</p>	<p>Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p>	<p>Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>1 infection found triple therapy with telaprevir to be associated with a higher likelihood of SVR (pooled RR 1.48, 95% CI: 1.26 to 1.75; I₂=0.0%)</p> <ul style="list-style-type: none"> Absolute increase in SVR rate: 22% (95% CI 13 to 31). <p>Triple therapy with pegylated interferon, ribavirin, and telaprevir for 12 weeks vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> 1 trial of patients with genotype 1 infection found no difference in likelihood of SVR <p>SOE: Low</p> <p>Response guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by a response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin for an additional 12 or 36 weeks) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> 1 trial of patients with genotype 1 infection found response guided triple therapy with telaprevir to be associated with higher likelihood of SVR. Absolute increase in SVR rate: 25% to 31% 				

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>8 week telaprevir vs. 12 week teleprevir regimen:</p> <ul style="list-style-type: none"> 8 week regimen associated with a slightly lower SVR rate (69% vs. 75%) <p>Triple therapy with telaprevir for 48 weeks (12 weeks of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 36 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin) vs. triple therapy with telaprevir for 24 weeks (12 weeks of triple therapy followed by 12 weeks of dual therapy).</p> <ul style="list-style-type: none"> 1 trial of patients with genotype 1 found no difference in likelihood of SVR. 				
<p>Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir: Dose effects of Pegylated Interferon Alfa-2a vs. Alfa-2b and Duration effects</p> <p>Outcome: Sustained virologic response</p> <p>SOE: Low</p> <p>1 trial of response-guided triple therapy with telaprevir (24 or 48 weeks, based on absence or presence of HCV-RNA from weeks 4 through 20) found similar SVR rates (81–85%) for regimens that varied on telaprevir dose (750 mg tid vs. 1,125 mg</p>	<p>No new research was identified.</p>	<p>Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p>	<p>Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>bid) and type of pegylated interferon (alfa-2a or alfa-2b).</p> <p>1 trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92% and 88%) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy.</p>				current practice.
Not in original CER	<p>One RCT examined the new vaccine TG4040 and compared dual therapy with PEG-IFNα/RBV for 48 weeks (Group A) to triple therapy with PEG-IFNα/RBV for 4 weeks followed by PEG-IFNα/RBV for 44 weeks with 6 injections of TG4040 (Group B) to triple therapy with TG4040 for 12 weeks (7 injections) followed by PEG-IFNα/RBV for 48 weeks with 6 injections of TG4040 (Group C). Findings indicated that after 24 weeks, A higher percentage of patients</p>	None identified		

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
	<p>achieved a sustained virologic response 24 weeks after therapy ended in group C (58.2%) than in groups A (48.4%) or B (50.8%)</p>			
<p>Key Question 2b: How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?</p>				
<p>Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin Outcome: Sustained virologic response SOE: Low</p> <p>Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin:</p> <ul style="list-style-type: none"> • Largest trial (N=3,070) found no clear differences in relative risk estimates for SVR in genotype 1 patients stratified by race, sex, age, baseline fibrosis stage, or baseline viral load. • Characteristics associated with low absolute SVR rates: <ul style="list-style-type: none"> ○ Older age ○ Black race ○ Advanced fibrosis or cirrhosis ○ High baseline viral load <p>SOE: Moderate</p>	<p>No new research was identified.</p>	<p>None identified</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p>	<p>Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin:</p> <ul style="list-style-type: none"> • 4 trials found no clear differences in relative risk estimates for SVR in patients stratified by genotype. • Genotype 1 infection was associated with lower absolute SVR rate than genotypes 2 and 3. 				
<p>Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin Outcome: Sustained virologic response SOE: Moderate</p> <p>Triple therapy with boceprevir for 48 weeks (4 weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by 44 weeks of triple therapy with pegylated interferon, ribavirin, and boceprevir) (2 trials):</p> <ul style="list-style-type: none"> • Men vs. Women: No difference in relative risk estimates for SVR • Blacks vs. Non-Black patients: No clear difference in relative risk estimates. Black race associated with lower SVR. <p>Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin:</p>	<p>No new research was identified.</p>	<p>None identified</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p> <p>One reviewer provided a study examining triple therapy; however, this was not a comparative effectiveness study.⁸</p>	<p>Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<ul style="list-style-type: none"> 2 trials found triple therapy to be associated with a higher likelihood of achieving SVR in patients with high baseline HCV-RNA viral load (>600,000 or 800,000 IU/mL). Found no difference in likelihood of SVR in patients of lower viral load. 				
<p>Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin</p> <p>Outcome: Sustained virologic response SOE: Moderate (for age and sex); Low (for other factors)</p> <p>Response-guided triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided dual therapy with pegylated interferon alfa-2a and ribavirin) vs. dual therapy with pegylated interferon plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> 1 trial found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or BMI. Characteristics associated with lower absolute SVR rates: <ul style="list-style-type: none"> Older age Black race Advanced fibrosis or 	<p>No new research was identified.</p>	<p>Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p> <p>One reviewer provided a study examining triple therapy; however, this was not a comparative effectiveness study.⁸</p>	<p>Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>cirrhosis</p> <ul style="list-style-type: none"> ○ Higher BMI <p>24-week fixed duration triple therapy with telaprevir, pegylated interferon alfa-2b, and ribavirin vs. 48 weeks of dual therapy:</p> <ul style="list-style-type: none"> • 1 trial found no differences in estimates of effect in patients stratified by sex or age. <p>SOE: Insufficient</p> <p>Triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and telaprevir vs. dual therapy:</p> <ul style="list-style-type: none"> • 2 trials reported inconsistent findings for differential relative risk estimates according to baseline viral load. 				
<p>Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin</p> <p>Outcome: Harms</p> <p>SOE: Moderate</p> <p>Dual therapy with pegylated interferon alfa-2b vs. dual therapy with pegylated interferon alfa-2a plus ribavirin:</p> <ul style="list-style-type: none"> • Dual therapy with pegylated interferon alfa-2b was associated with: <ul style="list-style-type: none"> ○ Slightly greater risk of headache (3 trials), pooled RR 1.1, 95% CI 1.1 to 1.2; I₂=0%) 	<p>No new research was identified.</p>	<p>None identified</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p>	<p>Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<ul style="list-style-type: none"> ○ Lower risk of serious adverse events (2 trials), pooled RR 0.76; 95% CI 0.71 to 0.88; I₂=0%) ○ Lower risk of neutropenia (5 trials), pooled RR 0.61, 95% CI 0.46 to 0.83; I₂=38% ○ Lower risk of rash (2 trials), pooled RR 0.79, 95% CI 0.71 to 0.88; I₂=0.0%). • Found no difference in withdrawals due to adverse events. 				
<p>Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin</p> <p>Outcome: Harms SOE: Moderate</p> <p>Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) vs. dual therapy with pegylated interferon alfa-2b plus ribavirin:</p> <ul style="list-style-type: none"> • Triple therapy with boceprevir was associated with: <ul style="list-style-type: none"> ○ Increased risk of neutropenia (2 trials), pooled RR 1.8, 95% CI 1.5 to 2.3; I₂=0.0% ○ Dysgeusia (2 trials), 	<p>No new research was identified.</p>	<p>None identified</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p> <p>One reviewer provided a study examining triple therapy; however, this was not a comparative effectiveness study.⁸</p>	<p>Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>pooled RR 2.5, 95% CI 2.0 to 3.2; I₂=0.0%</p> <ul style="list-style-type: none"> ○ Anemia (2 trials), pooled RR 2.0, 95% CI 1.4 to 2.8; I₂=0.0% ○ Thrombocytopenia (2 trials), pooled RR 3.2, 95% CI 1.2 to 8.2; I₂=0.0% <ul style="list-style-type: none"> • % Incidence in triple therapy: <ul style="list-style-type: none"> ○ Anemia: 25% ○ Neutropenia: 33% ○ Severe anemia: 4-5% ○ Severe neutropenia: 8-15% 				
<p>Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin</p> <p>Outcome: Harms SOE: Moderate</p> <p>12-week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2a plus ribavirin:</p> <ul style="list-style-type: none"> • 2 trials found no statistically significant difference in risk of any assessed adverse event. <p>24-week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon</p>	<p>No new research was identified.</p>	<p>Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p> <p>One reviewer provided a study examining triple therapy; however, this was not a comparative effectiveness study.⁸</p>	<p>Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>alfa-2a plus ribavirin for 12 weeks) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> • 3 trials found triple therapy to be associated with: <ul style="list-style-type: none"> ○ Increased risk of anemia (3 trials), pooled RR 1.3, 95% CI 1.1 to 1.5; I₂=0.0% ○ Rash (3 trials), pooled RR 1.4, 95% CI 1.1 to 1.7, I₂=0.0% • Patients randomized to the telaprevir therapy experienced: <ul style="list-style-type: none"> ○ Rash (1 to 2/3 of entire group) ○ Anemia: 27-91% ○ Severe rash: 7-10% ○ Severe anemia: 4-11% • No difference in risk of withdrawal due to adverse events. <p>SOE: Low</p> <p>Response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided duration pegylated interferon alfa-2a and ribavirin) vs. therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks:</p> <ul style="list-style-type: none"> • 1 trial found association between triple therapy and: <ul style="list-style-type: none"> ○ Increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI 				

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
<p>2.6 to 5.7)</p> <ul style="list-style-type: none"> ○ Anemia(38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5) ○ Any rash (36% vs. 24%, RR 1.5, 95% CI 1.2 to 1.8) ○ Severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13) 				
Key Question 3. Do these harms differ according to patient subgroup characteristics?				
<p>Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin</p> <p>Outcome: Harms SOE: Insufficient</p> <p>Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin:</p> <ul style="list-style-type: none"> • No trials reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. • 3 trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials. 	<p>No new research was identified.</p>	<p>None identified</p>	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p> <p>One⁹ reviewer provided a study comparing PEG-IFN alfa-2a (180 µg/week; n=402) to PEG-IFN alfa-2b (1.5 µg/kg/week; n=259) with ribavirin (800–1200 mg/day) for 24 or 48 weeks in Korea, and found that unlike the Western data, efficacy and safety of PEG-IFN alfa-2a were similar to those of PEG-IFN alfa-2b in chronically HCV-infected Korean patients regardless of</p>	<p>Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
			age, HCV viral load, and hepatic fibrosis.	
<p>Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir or Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin Outcome: Harms SOE: Insufficient</p> <p>Triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir vs. dual therapy with pegylated interferon plus ribavirin:</p> <ul style="list-style-type: none"> No trial evaluated harms in patient subgroups. All trials evaluated patients with genotype 1 infection. 	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."	<p>All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.</p> <p>One reviewer provided a study examining triple therapy; however, this was not a comparative effectiveness study.⁸</p>	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.
Key Question 4. Have improvements in intermediate outcomes been shown to reduce the risk or rates of adverse health outcomes from HCV infection?				
<p>Outcome: Mortality and long-term hepatic complications SOE: Moderate</p> <p>SVR after antiviral therapy vs. no SVR:</p> <ul style="list-style-type: none"> 1 large VA hospital study found SVR after antiviral therapy to be associated with lower risk of all-cause mortality (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."	Two reviewers agreed that the conclusions in the original CER were current. One reviewer noted that the conclusions were partially current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and

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<p>0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively).</p> <ul style="list-style-type: none"> 18 cohort studies found SVR to be associated with decreased risk of all-cause mortality, liver-related mortality, HCC, and other complications of ESLD Studies had methodological shortcomings, including inadequate handling of confounders. 10 were conducted in Asia. 				<p>pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>
<p>Outcome: Short-term quality of life SOE: Low</p> <p>SVR vs. no SVR:</p> <ul style="list-style-type: none"> 9 studies found SVR to be associated with greater improvement in measures related to QoL (generic or disease-specific) 24 weeks after the end of antiviral treatment. <ul style="list-style-type: none"> Differences averaging 5 to 10 points on various SF-36 domains. All studies were poor-quality and were characterized by failure to adjust for confounders, high loss to follow-up, and failure to blind patients to SVR status. 	<p>No new research was identified.</p>	<p>Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions...including Stevens Johnson Syndrome..."</p>	<p>Two reviewers agreed that the conclusions in the original CER were current. One reviewer noted that the conclusions were partially current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S. One reviewer noted that there is markedly new evidence regarding quality of life associated with new direct acting antivirals. Two studies were provided; however, were not comparative effectiveness studies, thus did not meet inclusion criteria.^{6,7}</p>	<p>Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.</p>

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment

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