WHO/HIV/2014.42

Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle-income countries
PICO 7 Treatment (Simeprevir) – Decision Making Table

Evidence to recommendation framework

Should simeprevir be used to treat chronic hepatitis C?

Problem: HCV genotype 1 infection
Option: simprevir + peg-INF + ribavirin
Comparison: peg-INF + ribavirin
Setting: ambulatory care
Perspective: WHO

Background: [Background]

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	HCV affects 170 million people around the world; 3% of the world's population.	

Date: **2013-12-07**

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☒ *No known undesirable outcomes* ☐
Are the desirable anticipated effects large?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | ***Varies*** ☐
Are the undesirable anticipated effects small?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ | ***Varies*** ☐
Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | ***Varies*** ☐

RESEARCH EVIDENCE

Summary of findings: *simeprevir (12 weeks)/PR (24-48 weeks) vs. PR*

Outcome	Without SMV (per 1000)	With SMV (per 1000)	Difference (per 1000 (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)
Failure of SVR	544	212	**332 less**	**RR 0.39** (0.33 to 0.45)	HIGH
SAE leading to treatment discontinuation	17	19	**2 more**	**RR 1.13** (0.5 to 2.55	MODERATE due to imprecision

Link to detailed evidence profile

ADDITIONAL CONSIDERATIONS

Patients with HCV genotype 1a should be screened for the genetic mutation Q80K polymorphism (30% of genotype 1a patients in the studies), as the response in those patient is not much higher than with peg-IFN alone.

The response rate in HIV co-infected patients was 74% (78/106) [Dietrich et al; EACS 2013; not included in this analysis as no peg-INF/RBV comparator group was included], similar to what was observed in non-HIV co-infected patients. The findings can therefore be applied to a HIV co-infected population without rating down for indirectess.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	At the time of deliberations, detailed pricing information was unavailable for countries covered in this guideline.	
	Is the incremental cost small relative to the net benefits?	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐		
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☐ *Uncertain* ☒ *Probably reduced* ☐ *Reduced* ☐ ***Varies*** ☐		
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐		
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	No refrigeration necessary; once daily dosing	

Date: 2013-12-03

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	Simeprevir (12 weeks), given in combination with pegylated interferon and ribavirin (for 24 weeks) is recommended in genotype 1 HCV infection without Q80K polymorphism (non-HIV co-infected and HIV co-infected populations) rather than pegylated interferon and ribavirin alone. Strong recommendation, high quality of evidence Note: This recommendation was made without explicit resource use considerations as detailed pricing information was unavailable for countries covered in this guideline at the time of deliberations.
Justification	[to follow]
Subgroup considerations	none
Implementation considerations	[to follow]
Monitoring and evaluation	[to follow]
Research priorities	[to follow]

Evidence profile title: Should simeprevir/ribavirin/peg-INF vs. peg-IFN/ribavirin be used for HCV genotype 1 infection*?

Author(s): YFY
Date: 2013-12-09

Question: Should simeprevir (12 weeks)/ribavirin/peg-INF (24 weeks) vs. peg-IFN/ribavirin be used for HCV genotype 1 infection*?

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Peg-IFN/ribavirin	With Simeprevir/ribavirin/ peg-INF		Risk with Peg-IFN/ribavirin	Risk difference with Simeprevir/ribavirin/peg-INF (95% CI)
Failure of SVR (CRITICAL OUTCOME)											
1464 (5 RCT)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨁ **HIGH** large effect present	294/540 (54.4%)	193/924 (20.9%)	**RR 0.39** (0.33 to 0.45)	**544 SVR failures per 1000**	**332 fewer SVR failures per 1000** (from 299 fewer to 365 fewer)
SAE leading to treatment discontinuation (initial 12 weeks) (IMPORTANT OUTCOME)											
1464 (5 RCT) (data from FDA briefing)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⨁⨁⨁⊖ **MODERATE**[1] due to imprecision	9/540 (1.7%)	15/924 (1.6%)	**RR 1.13** (0.5 to 2.55)	**17 SAE per 1000**	**2 more SAE per 1000** (from 8 fewer to 26 more)

[1] Estimate crosses one; large confidence interval (fails to exclude relative harms as well as benefits)

* Patients with HCV genotype 1a should be screened for the genetic mutation Q80K polymorphism (30% of genotype 1a patients in the studies), as the response in those patient is not much higher than with peg-IFN alone. The response rate in HIV co-infected patients was 74% (78/106) [Dietrich et al; EACS 2013; not included in this analysis as no peg-INF/RBV comparator group included], similar to what was observed in non-HIV co-infected patients.

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References

(To make references appear here, place cursor in any text above this page and choose: Insert > Footnote…> Endnote > End of section)

Definitions for ratings of the certainty of the evidence (GRADE)**

Ratings	Definitions	Implications
⨁⨁⨁⨁ High	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low.	This evidence provides a very good basis for making a decision about whether to implement the intervention. Impact evaluation and monitoring of the impact are unlikely to be needed if it is implemented.
⨁⨁⨁◯ Moderate	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[4] is moderate.	This evidence provides a good basis for making a decision about whether to implement the intervention. Monitoring of the impact is likely to be needed and impact evaluation may be warranted if it is implemented.
⨁⨁◯◯ Low	This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[4] is high.	This evidence provides some basis for making a decision about whether to implement the intervention. Impact evaluation is likely to be warranted if it is implemented.
⨁◯◯◯ Very low	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[4] is very high.	This evidence does not provide a good basis for making a decision about whether to implement the intervention. Impact evaluation is very likely to be warranted if it is implemented.

*Substantially different: large enough difference that it might have an effect on a decision

**The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of present grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations. Many international organizations have provided input into the development of the approach and have started using it.

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