Eradication of chronic hepatitis C virus (HCV) infection and the development of hepatocellular carcinoma (HCC): a meta-analysis of observational studies

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BACKGROUND

Rationale

- HCV is a leading cause of HCC, which occurs in approximately 15,000 persons annually in the United States.¹
- Antiviral therapy for HCV can result in eradication of the virus (i.e., absence of detectable HCV RNA) after treatment, known as sustained virologic response (SVR).²
- Persons who achieve an SVR have a lower risk of developing HCC and liver-related mortality.
- Recent advances in HCV antiviral treatments, including the FDA approval of telaprevir and boceprevir, are making the achievement of SVR possible for the majority of patients undergoing therapy.⁴

Purpose

 To determine the association between achievement of SVR and the development of HCC among HCV-infected persons.

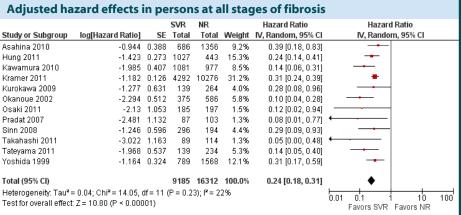
METHODS

- A systematic review and meta-analysis, conducted using MEDLINE, EMBASE, CINAHL, the Cochrane Library, Sociological Abstracts, and DARE, examined the development of HCC among HCV-infected persons at all stages of fibrosis or with advanced liver disease (Metavir F3-F4 or Ishak 4-6) achieving SVR or not responding to treatment.
- English-language, observational studies targeting an adult population and with an average follow-up of at least two years were included.
- Two independent investigators reviewed and abstracted full articles.
- The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to determine overall study quality.
- Pooled estimates (hazard ratios and incidence rates) were obtained through randomeffects meta-analysis using the inverse-variance method.

Study Flow Chart decords identified through database searches (n = 10,580)MEDLINE: 3.275 EMBASE: 3,439 Web of Science: 3.317 DARE: 152 The Cochrane Library: 199 Excluded duplicates (n = 4.172)Records screened Excluded Additional records identified Did not meet (n = 6,112)Full-text articles assessed for (n = 309)Excluded (n = 279)Duplicative: 66 No SVR/NR data: 114 Editorial/review article: 31 Appropriate outcome not reported: 17 Did not meet inclusion criteria: 37 Included studies Incomplete information: 14

RESULTS

- Thirty observational studies met inclusion criteria, 18 of which provided adjusted effect estimates were used to calculate the pooled relative risk.
- Among HCV-infected persons with advanced liver disease, achievement of SVR significantly reduces the risk of HCC development by approximately 77% (HR=0.23 [95% CI, 0.16 to 0.35]; moderate quality evidence). Similarly, the relative risk reduction among HCV-infected persons at any stage of disease progression was estimated at 76% (HR=0.24 [95% CI, 0.18 to 0.31]; moderate quality evidence).
- Pooled annual incidence of HCC development among persons with advanced liver disease not responding to treatment was 3.3% (95% CI, 2.6% to 4.2%). By comparison, HCC developed at rate of 1.0% (95% CI, 0.7-1.5%) annually among persons with advanced fibrosis who achieved SVR.
- Judgments on study risk of bias were determined to not reduce confidence in the estimate of effect. The final quality of evidence was upgraded to Moderate based on reported large relative effect.



Study or Subgroup log[Hazard Ratio] SE Total Weight V, Random, 95% CI W, Random, 95 Braks 2007 -1.966 0.601 37 76 11.2% 0.14 [0.04, 0.45] ————————————————————————————————————	CI		SVR NR Hazard Ratio									
Bruno 2007 -0.954 0.425 124 759 22.4% 0.39 [0.17, 0.89]		IV, Random, 95% CI	IV, Random, 95% CI	Study or Subgroup log[Hazard Ratio] SE Total Total Weight IV, Random, 95% (
Cardoso 2010 -1.12 0.514 103 204 15.3% 0.33 [0.12, 0.89]			0.14 [0.04, 0.45]	11.2%	76	37	0.601	-1.966	Braks 2007			
Hasegawa 2007 -1.69 0.755 48 57 7.1% 0.18 [0.04, 0.81]			0.39 [0.17, 0.89]	22.4%	759	124	0.425	-0.954	Bruno 2007			
Hung 2006 -1.468 0.622 73 59 10.4% 0.23 (0.07, 0.78) Morgan 2010 -1.721 0.764 140 309 6.9% 0.18 (0.04, 0.80)			0.33 [0.12, 0.89]	15.3%	204	103	0.514	-1.12	Cardoso 2010			
Morgan 2010 -1.721 0.764 140 309 6.9% 0.18 [0.04, 0.80]			0.18 [0.04, 0.81]	7.1%	57	48	0.755	-1.69	Hasegawa 2007			
			0.23 [0.07, 0.78]	10.4%	59	73	0.622	-1.468	Hung 2006			
Van der Meer 2012 -1.592 0.416 192 338 23.4% 0.20 [0.09, 0.46]			0.18 [0.04, 0.80]	6.9%	309	140	0.764	-1.721	Morgan 2010			
			0.20 [0.09, 0.46]	23.4%	338	192	0.416	-1.592	Van der Meer 2012			
Velosa 2011 -2.433 1.108 39 91 3.3% 0.09 [0.01, 0.77]			0.09 [0.01, 0.77]	3.3%	91	39	1.108	-2.433	Velosa 2011			
Total (95% CI) 756 1893 100.0% 0.23 [0.16, 0.35]		•	0.23 [0.16, 0.35]	100.0%	1893	756			Total (95% CI)			
Heterogeneity: Tau² = 0.00; Chi² = 3.64, df = 7 (P = 0.82); I² = 0%	10 100											

		Quality As	sessment	Summary of Findings					
GRADE Evidence	Outromo	Outcome Participants Overall		Study Event Rates, n/N (%)			Anticipated	icipated Absolute Effects	
	Outcome	(Studies), n	Quality of Evidence	Failed or No Treatment	Viral Eradication	Relative Effect	Risk with Failed or No Treatment	Absolute Effect with Viral Eradication (95% CI)	
ofile	HCC among Persons	25,906 (12)	Moderate	990/16,312 (6.1)	145/9,185	Adjusted HR:	All Stages of Fibrosis, per year	Fibrosis, per year	
offie	at all Fibrosis Stages				(1.6)	0.24 (0.18-0.31)	17 HCC per 1000	14 fewer HCC per 1000 (from 12 fewer to 15 fewer)	
	3.0-8.2 years follow-						Advanced Li	er Disease, per year	
	ир						33 HCC per 1000	23 fewer HCC per 1000 (from 18 fewer to 26 fewer)	

LIMITATIONS

- Excluded reports not written in English.
- Most studies were retrospective in nature; some publication bias possible.

CONCLUSIONS

- Achievement of SVR among persons infected with HCV at any fibrosis stage is associated with a significant relative risk reduction of developing HCC.
- Early treatment for HCV is essential in preventing the development of HCC.
- With the availability of newer and more effective therapies, SVR rates can be increased and HCC incidence rates can be reduced in the population of HCVinfected persons.

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