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Risk of late relapse or re-infection with Hepatitis C after Sustained Virological Response: meta-analysis of 66 studies in 11,071 patients

Andrew Hill[1], Bryony Simmons[2], Jawaad Saleem[2], and Graham Cooke[2]

[1] St Stephens AIDS Trust, Chelsea and Westminster Hospital, London, United Kingdom, [2] Faculty of Medicine, Imperial College London, London, United Kingdom

UNIVERSITY OF LIVERPOOL

Correspondence to:
Dr Andrew Hill PhD
Molecular and Clinical Pharmacology
1st Floor Block H, 70 Pembroke Place,
Liverpool, L69 3G
Tel:+44 7834 364 608
Email: microhaart@aol.com

Introduction

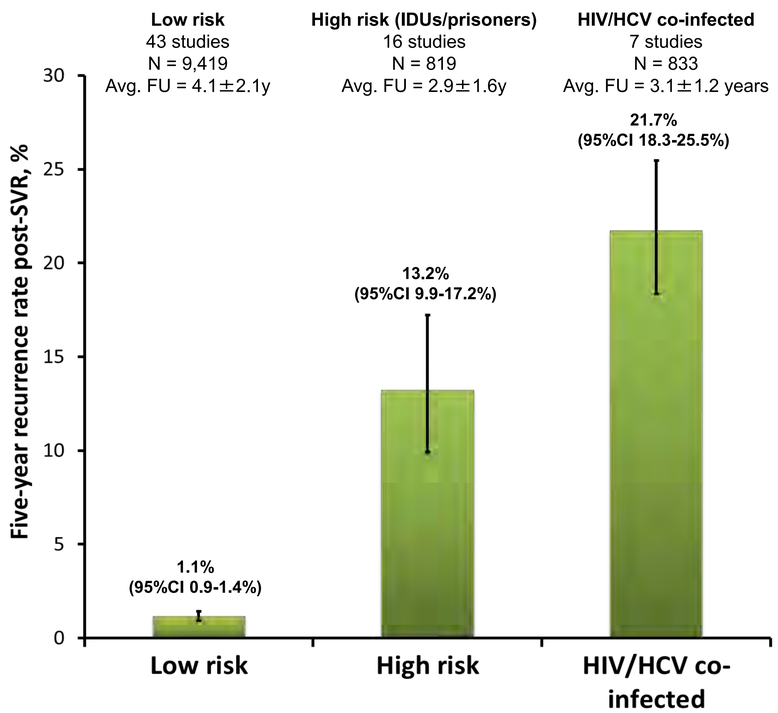
Combination treatment with direct acting antivirals can lead to a sustained virological response (SVR) in over 90% of people with Hepatitis C (HCV) infection. However, subsequent recurrence of HCV (either from late relapse or reinfection) reverses the beneficial effects of SVR. This analysis aimed to estimate the five-year risk of HCV late relapse or reinfection post-SVR, by risk group.

Methods

The MEDLINE and EMBASE databases were searched for studies analysing late relapse or reinfection with HCV post-SVR. SVR was defined as undetectable HCV RNA 24 weeks post-treatment, typically consisting of pegylated-interferon and ribavirin. All studies with >6 months of follow up post-SVR were included. Studies were categorised in to three groups: 1) Low risk population, inclusive of studies of mono-HCV patients with no risk factors for reinfection (i.e. not including patients co-infected with HIV, injecting drug user (IDU), or prisoners); 2) High risk population, inclusive of studies of IDUs or prisoners; and 3) HIV/HCV co-infected populations, inclusive of all studies of HIV/HCV co-infected persons, regardless of other risk factors. Studies of liver transplant patients were excluded from the analysis. Recurrence was defined as confirmed HCV RNA detectability post-SVR (at least 6 months after the end of treatment), which could be the result of a late relapse or HCV reinfection.

For each study the one-year HCV relapse/reinfection rate was calculated as the number of recurrence events per 100 person-years (PY). Exact 95% confidence intervals (95%CI) were calculated assuming a Poisson distribution. A pooled estimate of reinfection was calculated for each of the three groups. This pooled estimate was used to determine the five-year recurrence rate for each risk group.

Figure 1. Five-year rate (95%CI) of recurrence post-SVR, by risk group



Results

Results were available from 66 studies in 11,071 patients. In the 43 studies of HCV mono-infected "low risk" patients (n=9,419) there were 87 HCV recurrences during a mean 4.1 (±2.1) years of follow-up. The pooled estimate for the recurrence rate was 0.23/100PY (95%CI 0.18-0.28) for the low risk group, leading to a corresponding five-year recurrence rate of 1.14% (95%CI 0.92-1.41).

For the 16 studies of HCV mono-infected "high risk" patients (n=819) there were 53 HCV recurrences during a mean 2.9 (±1.6) years of follow-up. The pooled estimate for the HCV recurrence rate was 2.80/100PY(95%CI 2.06-3.71), leading to a five-year recurrence rate of 13.22% (95%CI 9.89-17.21).

For the 7 studies of HIV/HCV co-infected patients (n=833) there were 123 HCV recurrences during a mean 3.1 (±1.2) years of follow-up. The pooled recurrence rate was 4.78/100PY (95%CI 3.97-5.71), corresponding to a five-year HCV recurrence rate of 21.72% (95%CI 18.34-25.47). For the studies of HIV/HCV co-infected patients, five-year rates of HCV recurrence were significantly lower for patients followed up after randomised clinical trials, compared to unselected patients cohorts (1.44% [95%CI 0.05-7.82] vs. 24.57% [95%CI 20.79-28.72]). Further exploration is required to determine whether recurrence rates in this population are due to HIV co-infection or risk behaviours, or an interaction between both.

Table 1. Risk of HCV recurrence post-SVR, for three groups of patients

High Risk patients	Country, risk factor	Recurrence /SVR[a]	Follow-up, yrs (PYFU)	Recurrence rate/100PY (95%CI)[b]
Ruzic 2013	Serbia, IDU	0/20	5.0 (100.0)	0.0 (0.0-3.7)
Conway 2010	Canada, IDU	0/23	0.9 (19.7)	0.0 (0.0-18.7)
Grady 2012	Netherlands, IDU	1/42	2.0 (131.6)	0.8 (0.0-4.2)
Dalgard 2002	Norway, IDU	1/27	4.8 (129.6)	0.8 (0.0-4.3)
Weir 2014	Scotland, IDU	7/277	4.5 (410.0)	1.7 (0.7-3.5)
Edlin	Spain, Prisoners	1/15	(45.1)	2.2 (0.1-12.4)
Currie 2008	USA, IDU	1/9	3.6 (38.0)	2.6 (0.1-14.7)
Hilsden 2013	Canada, IDU	1/23	1.8 (35.7)	2.8 (0.1-15.6)
Grebely 2010	Canada, IDU	2/35	2.0 (62.5)	3.2 (0.4-11.6)
Tsirogianni 2013	Greece, IDU	7/32	6.0 (192.0)	3.6 (1.5-7.5)
Backmund 2006	Germany, IDU	2/18	2.8 (48.8)	4.1 (0.5-14.8)
Manolakopoulos 2012	Greece, IDU	5/61	2.0 (122.0)	4.1 (1.3-9.6)
Bate 2010	Australia, Prisoners	9/53	3.4 (180.2)	5.0 (2.3-9.5)
Marco 2013	Spain, Prisoners	9/119	1.4 (170.5)	5.3 (2.4-10.0)
Deshaies 2013	Canada, IDU	2/20	1.6 (31.7)	6.3 (0.8-22.8)
Grebely 2012	Australia, IDU	5/45	1.2 (56.0)	8.9 (3.7-21.4)
Total		**53/819**	**2.9 (1773)[c]**	**2.80% (2.06-3.71%)**

HIV/HCV co-infected	Country, risk factor	Recurrence /SVR[a]	Follow-up, yrs (PYFU)	Recurrence rate/100PY (95%CI)[b]
Soriano 2004	Spain, mixed (no IDU)	0/77	4.8 (372.2)	0.0 (0.0-1.0)
Swain 2010* (combination therapy)	Multicentre, mixed	0/72	3.5 (251.4)	0.0 (0.0-1.5)
Swain 2010* (monotherapy)	Multicentre, mixed	1/28	3.5 (93.7)	1.1 (0.0-5.9)
Ingliz 2014 (w/o Martin)	Europe, mixed	69/455	3.1 (1412.1)	4.9 (3.8-6.2)
Martin 2013	UK, MSM	27/114	2.4 (280.0)	9.6 (6.4-14.0)
Van Hommerig 2013	The Netherlands, MSM	6/18	3.3 (59.4)	10.1 (3.7-22.0)
Lambers 2011	The Netherlands, MSM	11/51	1.3 (72.2)	15.2 (7.6-27.3)
Micallef 2007	Australia, mixed	9/18	1.2 (29.0)	31.0 (14.2-58.9)
Total		**123/833**	**3.1 (2570)[c]**	**4.78% (3.97-5.71%)**

Abbreviations: IDU, injecting drug user; MSM, men who have sex with men
*HIV/HCV studies marked with an asterisk are RCTs
[a]No. of re-infections or relapse/no. of individuals in study achieving SVR;
[b]Upper CI one-sided 97.5% CI if events equals zero; [c]Mean follow-up (total PYFU)

Conclusions

In this analysis the 5-year rate of HCV recurrence (late relapse /re-infection) post-SVR was:

1.14% (95%CI 0.92-1.41) in HCV mono-infected "low risk" patients,

13.22% (95%CI 9.89-17.21) in HCV mono-infected IDUs / prisoners

21.72% (95%CI 18.34-25.47) in HIV/HCV co-infected patients.

The large differences in event rates by risk group suggest that re-infection is significantly more common than late relapse.

Low Risk patients	Country	Recurrence /SVR[a]	Follow-up, yrs (PYFU)	Recurrence rate/100PY (95%CI)[b]
Choi 2011	South Korea	0/224	1.5 (336.0)	0.0 (0.0-1.1)
Trapero-Marugan 2011	Spain	0/153	6.3 (969.0)	0.0 (0.0-0.4)
Formann 2006	Austria	0/187	2.4 (451.9)	0.0 (0.0-0.8)
Maylin 2008	France	0/344	3.3 (1124.9)	0.0 (0.0-0.3)
da Costa Ferreira 2010	Brazil	0/174	3.9 (681.5)	0.0 (0.0-0.5)
Hofer 2009	Europe	0/251	4.2 (1045.8)	0.0 (0.0-0.4)
Papastergiou 2011	Greece	0/144	3.3 (480.0)	0.0 (0.0-0.8)
Morisco 2011	Italy	0/150	8.6 (1290.0)	0.0 (0.0-0.3)
Barnard 2012	NR	1/808	3.0 (2424.0)	0.0 (0.0-0.2)
Kim 2010	South Korea	0/37	1.0 (37.0)	0.0 (0.0-10.0)
Adamek 2007	Poland	0/78	1.8 (142.4)	0.0 (0.0-2.6)
Giordanino 2014	Italy	0/115	8.7 (1000.5)	0.0 (0.0-0.4)
Maruoka 2012	Japan	0/207	7.5 (1552.5)	0.0 (0.0-0.2)
Tsuda 2004	Japan	0/38	5.7 (216.6)	0.0 (0.0-1.7)
George 2009	USA	0/147	4.6 (673.8)	0.0 (0.0-0.5)
Ponsoda 2002	France	0/125	1.2 (145.8)	0.0 (0.0-2.5)
Hotho 2013	Netherlands	0/19	1.8 (33.3)	0.0 (0.0-11.1)
Chavalitdhamrong 2006	Thailand	0/171	2.5 (421.5)	0.0 (0.0-0.9)
Papastergiou 2013	Greece	1/145	5.7 (831.3)	0.1 (0.0-0.7)
Koh 2013	USA	3/103	7.5 (772.5)	0.1 (0.0-0.7)
Manns 2013 (IFN)	Multicentre	6/636	4.9 (3141.8)	0.2 (0.1-0.4)
Manns 2013 (Peg-IFN)	Multicentre	3/366	4.1 (1487.8)	0.2 (0.0-0.6)
Morgan 2010	USA	1/91	6.6 (596.1)	0.2 (0.0-0.9)
Howe 2015	Multicentre	4/696	3.4 (2227.2)	0.2 (0.0-0.5)
Yu 2005	Taiwan	1/64	6.8 (435.8)	0.2 (0.0-1.3)
McHutchison 2006	Multicentre	5/492	5.4 (2667.4)	0.2 (0.1-0.4)
Lindsay 2008	Multicentre	4/366	4.8 (1738.9)	0.2 (0.1-0.6)
Desmond 2006	Australia	1/147	2.3 (338.1)	0.3 (0.0-1.6)
Giannini 2010	Italy	2/231	3.1 (725.7)	0.3 (0.0-1.0)
Puig-de-Castillo 2011	Spain	1/80	5.0 (400.0)	0.3 (0.0-1.4)
Torres Ibarra 2013	Mexico	3/188	5.2 (987.0)	0.3 (0.1-0.9)
Swain 2010	Multicentre	11/1243	3.4 (4226.2)	0.3 (0.1-0.5)
Ignatova 2013	Russia	3/208	4.7 (972.4)	0.3 (0.1-0.9)
Uyanikoglu 2013	Turkey	2/196	2.8 (547.2)	0.4 (0.0-1.3)
Ruiz-Antoran 2013	Spain	1/62	2.5 (155.0)	0.6 (0.0-3.6)
Kim 2009	South Korea	1/73	1.4 (101.1)	1.0 (0.0-5.5)
Doyle (pos)	Australia	4/50	7.2 (360.0)	1.1 (0.3-2.8)
Rutter 2013	Multicentre	2/103	1.8 (180.3)	1.1 (0.1-4.0)
Veldt 2004	Europe	12/286	2.9 (834.2)	1.4 (0.7-2.5)
Rahman 2013	Bangladesh	4/52	5.0 (260.0)	1.5 (0.4-3.9)
Reichard 1999	Sweden	2/26	4.9 (127.4)	1.6 (0.2-5.7)
Fontaine 2000	France	1/44	1.0 (45.5)	2.2 (0.1-12.2)
Sood 2010	India	8/100	2.9 (285.3)	2.8 (1.2-5.5)
Total		**87/9419**	**4.1 (37,471)[c]**	**0.23% (0.18-0.28%)**

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