



Advanced liver disease outcomes after Hepatitis C viral eradication according to Human Immunodeficiency Virus coinfection in PITER cohort

MG Quaranta¹, L Ferrigno¹, M Monti², R Filomia³, E Billotti⁴, A Iannone⁵, G Migliorino⁶, B Cocco⁷, F Morisco⁸, M Vinci⁹, R D'Ambrosio¹⁰, L Chemello¹¹, M Massari¹², D Deluzzi¹³, FP Russo¹⁴, P Blanc¹⁵, G Verucchi¹⁶, M Puoti¹⁷, MG Rumi¹⁷, F Barbaro¹¹, TA Santantonio¹⁸, A Federico¹⁹, L Chessa²⁰, I Gentile⁸, M Zuin²¹, G Parruti²², G Morsica²³, LA Kondili¹ on behalf of PITER Collaborating Group*

1Istituto Superiore di Sanità, Rome, 2University of Florence, Florence, 3University Hospital of Messina, Messina, 4Sapienza University, Rome, 5University of Bari, Bari, 6San Gerardo Hospital, Monza, 7University Hospital of Pisa, Pisa, 8Federico II University, Naples, 9Niguarda Hospital, Milan, 10Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico, University of Milan, Milan, 11University Hospital of Padua, Padua, 12Azienda Unità Sanitaria Locale - IRCCS di Reggio Emilia, Reggio Emilia, 13University Hospital of Verona, Verona, 14University of Padua, Padua, 15Santa Maria Annunziata Hospital, Florence, 16Alma Mater Studiorum Bologna University, Bologna, 17University of Milan, Milan, 18Ospedali Riuniti, Foggia, 19University of Campania "Luigi Vanvitelli", Naples, 20University Hospital, Monserrato, Cagliari, 21San Paolo Hospital, University of Milan, 22Spirito Santo General Hospital, Pescara, 23San Raffaele Hospital, Milan. *available at www.progettopiter.it

Introduction/Summary

- Worldwide, approximately 2.3 million people are co-infected with Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV), giving rise to a global coinfection prevalence in HIV infected individuals of 6.2% (1). It is known that HIV accelerates the course of HCV-related chronic liver disease.
- The development of direct-acting antivirals (DAA) for HCV has revolutionized the treatment of HCV, including its treatment in patients with HIV coinfection (2). However, little is known about whether HIV coinfection modifies outcomes of HCV-related liver disease after achieving SVR.
- The aim of the present analysis was to evaluate the sociodemographic and clinical profile of HCV/HIV coinfecting versus HCV mono-infected patients in a real-life patients' cohort with the final goal to prospectively evaluate the clinical impact of DAA treatment in patients with progressive/severe liver disease according to HIV coinfection status.

Study Design

- The study population consisted of patients with chronic HCV infection consecutively enrolled in Piattaforma Italiana per lo studio della Terapia delle epatiti Virali (PITER) between April 2014 and June 2019, who were not receiving HCV treatment at the time of inclusion, and could be considered representative of the HCV chronic infected population in care in Italy (3).

Methods

- Outcome variables. The study outcomes following HCV eradication were evaluated in DAA treated patients with pre-treatment diagnosis of liver cirrhosis excluding patients with a history of liver transplantation prior to treatment.
- Statistical analysis. Patient's main baseline characteristics were reported as median and range or as proportions (N and %) for continuous and categorical variables, respectively. The Mann-Whitney U test was used for continuous variables to assess differences between distribution, and the Chi-squared test was used for comparisons of proportions. A p-value of <0.05 was considered statistically significant.

Variables independently associated to HCC incidence, the appearance of a decompensating event and changes in Child-Pugh (C-P) class, after the end of treatment were evaluated by Cox proportional hazard models.

In order to confirm the main results of the analyses, the propensity score was estimated using a nonparsimonious logistic regression model with the HIV infection as the dependent variable and all measured potential confounders as covariates. The following variables at baseline have been included: age, sex, BMI, alcohol, ALT, AST, platelets, albumin, bilirubin, INR, genotype, diabetes, anti-HBc, HBsAg, previous Interferon, HCC. Relationship between each outcome and HIV adjusted by propensity score was evaluated by multiple Cox regression analyses

All analyses were performed using the STATA/SE 15.1 statistical package (StataCorp LP, College Station, TX, USA).

Reference

- Platt L, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis.* 2016;16:797-808.
- Meissner EG. Update in HIV/HCV Co-Infection in the Direct Acting Antiviral Era. *Curr Opin Gastroenterol.* 2017;33(3):120-27.
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Results

Baseline clinical characteristics

- Coinfected and mono-infected patients were evaluated during a median follow-up of 27.1 (range 6-44.6) and 24.7 (range 6.8-47.5) months after viral eradication, respectively.
- Coinfected patients were observed to have a significantly younger age (median age of 52.5 vs 64 years, p<0.001) and increased liver disease severity in terms of C-P class distribution (A5: 52.7% vs 69.5%; A6: 18.9% vs 22.1%; B7: 16.2% vs 5.3%; B8: 10.8% vs 2.6%), compared to HCV mono-infected patients (p<0.001). A higher prevalence of HCC was observed in the coinfecting compared to mono-infected patients (6.3% vs 0.9%; p<0.05). HBsAg positivity was detected in 4 (3.7%) coinfecting and in 15 (1.2%) mono-infected patients (p<0.05). A decompensating event occurred prior to treatment in 15 (13.9%) and in 133 (10.7%) coinfecting and mono-infected patients, respectively (p>0.05).

Table 1. Baseline characteristics of the study population

Quantitative variables	HCV/HIV co-infected (N=1087 - SVR 93.9%)		HCV mono-infected (N=1242* - SVR 94.1%)		p**	
	Median	Range	Median	Range		
Age (years)	52.5	36-77	64.0	23-86	< 0.001	
ALT (IU/L)	60.0	10.0-268.0	74.0	10.0-797.0	< 0.05	
AST (IU/L)	60.0	17.0-371.0	70.0	13.0-652.0	> 0.05	
Platelets (x10 ⁹ /L)	105000	29000-150000	119000	51000-150000	> 0.05	
Albumin (g/dL)	3.9	2.8-5.1	3.9	2.1-7.3	> 0.05	
Bilirubin (mg/dL)	0.8	0.3-58.0	0.9	0.2-15.5	> 0.05	
INR	1.1	0.9-1.5	1.1	0.6-5.0	> 0.05	
Categorical variables						
Sex	N	%	N	%	p**	
Male	88	81	722	58.1	< 0.001	
Female	20	18.5	520	41.9		
BMI	Underweight	5	4.6	14	1.1	< 0.001
Normal	70	64.8	514	41.4		
Overweight	25	23.2	550	44.3		
Obese	8	7.4	163	13.1		
Alcohol use	Never	50	52.1	803	66.0	< 0.001
Current	26	27.1	116	9.5		
Past	20	20.8	297	24.4		
Genotype	nd	0	0.0	9	< 0.001	
1 (non subtype)	5	4.6	27	2.2		
1a	33	30.6	170	13.7		
1b	15	13.9	665	53.5		
2	4	3.7	168	13.5		
3	31	28.7	120	9.7		
4	20	18.5	83	6.7		
5	0	0.0	0	0.0		
Diabetes	Yes	16	14.8	259	20.9	> 0.05
No	92	85.2	983	79.2		
Anti-HBc	Yes	48	44.4	274	22.1	< 0.001
No	60	55.6	968	77.9		
HBsAg	Yes	4	3.7	15	1.2	< 0.05
No	104	96.3	1227	98.8		
Previous Interferon	Yes	30	27.8	415	33.4	> 0.05
No	78	72.2	827	66.6		
HCC	Yes	1	0.9	78	6.3	< 0.05
No	107	99.1	1164	93.7		
Decomp. cirrhosis	Yes	15	13.9	133	10.7	> 0.05
No	93	86.1	1109	89.3		
Child-Pugh score						
A-5	39	52.7	762	69.5		
A-6	14	18.9	242	22.1		
B-7	12	16.2	58	5.3		
B-8	8	10.8	28	2.6		
B-9	0	0.0	6	0.6		
C-10	1	1.4	0	0.0		
C-11	0	0.0	0	0.0		

* For some variables inconsistencies are due to missing values
 ** p value Mann-Whitney rank-sum test
 *** p value Chi-square test
 EOT: end of treatment

Results of 2

Clinical outcomes following SVR12 in patients with liver cirrhosis

Overall, no significant differences were observed among coinfecting and mono-infected patients for the different variables evaluated.

Table 2. Liver related outcomes following viral eradication

Outcome	HCV/HIV co-infected (N=1087)		HCV mono-infected (N=1242*)		p**
	N	%	N	%	
Cumulative HCC incidence	2	1.9	46	4.0	> 0.05
Liver transplant	3	1.1	23	1.9	> 0.05
C-P class increase*	3	5.4	84	8.2	> 0.05
Decompensating event	11	10.2	114	9.2	> 0.05

* For some variables inconsistencies are due to missing values
 ** p value Chi-square test
 * Excluding Child Pugh class C patients

Results of 3

Predictors of clinical outcomes following SVR12

Table 3. Variables associated with de-novo HCC occurrence. Univariate and multivariate analysis.

Baseline factors	Crude HR	95% CI	Adjusted HR	95% CI
HIV infection	0.44	0.11-1.81	0.50	0.06-4.48
Age (increasing years)	1.06	1.03-1.09	1.08	1.04-1.12
Sex (ref. female)	2.13	1.11-4.10	1.82	0.86-3.84
BMI: overweight/obese (ref. under-normalweight)	1.31	0.73-2.36	1.68	0.85-3.32
Current/past alcohol use (ref. never)	1.84	1.04-3.26	2.20	1.11-4.39
ALT (increasing IU/L)	1.00	0.99-1.00	1.00	0.99-1.01
AST (increasing IU/L)	1.00	0.99-1.01	1.01	0.99-1.02
Platelets (>100,000/uL)	1.47	0.83-2.61	0.83	0.43-1.61
Albumin (decreasing g/dL)	4.33	2.32-8.07	3.93	1.86-8.30
Bilirubin (increasing mg/dL)	1.01	0.93-1.11	1.04	0.92-1.17
INR (increasing unit)	1.16	0.38-3.53	0.95	0.23-3.93
Genotype (3 vs others)	1.36	0.61-3.04	2.99	1.07-8.37
Diabetes	1.31	0.68-2.51	1.27	0.63-2.58
Anti-HBc+	2.01	1.13-3.58	1.89	1.00-3.58
Previous Interferon	1.04	0.58-1.89	1.37	0.73-2.58
Previous decompensating event	1.29	0.55-3.03	0.50	0.43-2.95

Table 4. Variables associated with C-P class increase. Univariate and multivariate analysis.

Baseline factors	Crude HR	95% CI	Adjusted HR	95% CI
HIV infection	0.50	0.21-2.15	0.50	0.15-1.58
Age (increasing years)	1.00	0.98-1.02	1.00	0.98-1.02
Sex (ref. female)	1.77	1.12-2.81	2.01	1.19-3.40
BMI: overweight/obese (ref. under-normalweight)	0.88	0.58-1.34	0.77	0.50-1.20
Current/past alcohol use (ref. never)	0.99	0.63-1.55	0.77	0.47-1.25
ALT (increasing IU/L)	1.00	0.99-1.00	1.00	0.99-1.01
AST (increasing IU/L)	1.00	0.99-1.00	0.99	0.98-1.00
Platelets (ref. >100,000/uL)	2.01	1.31-3.08	1.88	1.17-3.03
Albumin (decreasing g/dL)	1.57	0.99-2.43	1.39	0.85-2.29
Bilirubin (increasing mg/dL)	0.99	0.87-1.12	0.86	0.62-1.20
INR (increasing unit)	2.15	1.45-3.19	2.34	1.47-3.71
Genotype (3 vs others)	1.51	0.80-2.84	1.55	0.75-3.17
Diabetes	1.14	0.69-1.89	0.95	0.56-1.61
Anti-HBc+	1.02	0.63-1.65	1.05	0.63-1.72
Previous Interferon	0.92	0.52-1.29	0.75	0.47-1.21
HCC	2.32	1.20-4.49	1.87	0.86-4.05
Previous decompensating event	1.97	1.17-3.31	1.28	0.70-2.35

Table 5. Variables associated with decompensating event. Univariate and multivariate analysis.

Baseline factors	Crude HR	95% CI	Adjusted HR	95% CI
HIV infection	1.07	0.58-1.99	0.68	0.25-1.82
Age (increasing years)	1.01	0.99-1.02	1.01	0.99-1.04
Sex (ref. female)	1.52	1.04-2.21	1.41	0.88-2.27
BMI: overweight/obese (ref. under-normalweight)	1.09	0.76-1.55	1.11	0.73-1.70
Current/past alcohol use (ref. never)	1.17	0.81-1.70	1.01	0.64-1.60
ALT (increasing IU/L)	0.99	0.99-0.99	1.00	0.99-1.01
AST (increasing IU/L)	1.00	0.99-1.00	1.00	0.99-1.01
Platelets (ref. >100,000/uL)	2.80	1.95-4.03	2.05	1.29-3.25
Albumin (decreasing g/dL)	5.17	3.54-7.55	1.99	1.25-3.17
Bilirubin (increasing mg/dL)	1.01	0.95-1.08	0.83	0.63-1.08
INR (increasing unit)	2.16	1.56-2.98	1.70	0.91-3.17
Genotype (3 vs others)	1.38	0.83-2.31	1.22	0.58-2.58
Diabetes	1.56	1.06-2.30	0.82	0.50-1.34
Anti-HBc+	0.69	0.44-1.08	0.78	0.46-1.32
Previous Interferon	0.79	0.54-1.17	0.79	0.50-1.26
HCC	2.59	1.48-4.51	2.02	1.04-3.92
Previous decompensating event	11.78	8.28-16.76	7.47	4.69-11.89

HIV coinfection was not associated with a higher probability of developing liver complications. The propensity score method was applied taking into account the different background between coinfecting and mono-infected groups, to ascertain the impact of HIV coinfection on liver disease outcomes. By Cox regression analyses, using HIV and propensity score as independent covariates, it was confirmed that neither de novo HCC appearance (HR=0.72; 95% CI 0.09-6.10) nor hepatic decompensation (HR=0.76; 95% CI 0.09-6.21) were influenced by HIV coinfection.

Conclusion

The results of the present study have shown that after successful DAA treatment, patients with advanced liver disease and HIV coinfection have a similar probability of developing liver complications as HCV mono-infected patients. Management of liver disease in HCV/HIV coinfecting patients with advanced liver disease who achieve SVR with DAA should not differ from that of HCV mono-infected patients.

"Curing" HCV is not the ultimate goal in patients with severe liver disease in both coinfecting and mono-infected patients. Once liver cirrhosis is established the risk of disease progression is decreased, but still persists regardless of viral eradication.