Impact of CMV on liver progression in HIV/HCV/CMV coinfected patients in a large cohort of HIV-infected patients

P228

Vita S[1], Lorenzini P[2], Lichtner M[1,3], Marchetti G[4], Mastroianni CM[5], Bandera A[6], Di Biagio A[7], Pinnetti C[2], Calcagno A[8], Castagna A[9], Antinori A[2], D'Arminio Monforte A[10]

[1)] SM Goretti Hospital Infectious Disease Unit, Latina, Italy;[2)] National Institute of Infectious Diseases ""Lazzaro Spallanzani"", Rome, Italy; [3)] Sapienza University of Rome, Polo pontino Latina, Italy; [4)] Clinic of Infectious Diseases, San Paolo Hospital, University of Milan, Milan, Italy;[5)] Sapienza University of Rome, Italy;[6)] Clinic of Infectious Diseases, "San Gerardo" Hospital - University of Milano-Bicocca, Monza, Italy; [7)] Infectious Diseases Unit, Policlinico Hospital San Martino, Genoa, Italy; [8)] Infectious Diseases, University of Torino, Torino, Italy; [9)] Vita-Salute San Raffaele University, Milan, Italy; [10)] Infectious Diseases, Unit San Raffaele Hospital, Milan, Italy.

BACKGROUND

CMV seropositivity have been linked with Severe Non AIDS events/deaths and subclinical carotid artery disease in HIV-infected individuals [1,2]. CMV/HCV/HIV coinfected women, have been shown to display higher CMV IgG levels versus HIV mono-infected; likewise HIV/HCV/CMV co-infected patients have higher HCV viral load, suggesting a persistent interaction between viruses [3].

AIMS

We evaluated prevalence and impact of CMV-Ab on liver progression, AIDS events and Severe Non AIDS events/deaths in HIV/HCV/CMV coinfected subjects in the ICONA cohort.

STUDY DESIGN AND METHODS

The ICONA foundation study cohort is an observational multicentre cohort of individuals infected with HIV. We included patients from ICONA with ≥1 CMV-IgG and HCV-Ab available, at least 1 follow-up visit and no ESLD (End Stage Liver Disease) at baseline.

Four different outcomes were studied:

1)ESDL;

2)ESLD+fib4>3.25;

3)AIDS-defining event/ AIDS-related death

4)Severe Non AIDS events/ Non AIDS-related death

Severe non AIDS-related event included: cardio and cerebrovascular events (myocardial infaction, coronary bypass graft, conorary angioplastic, carotid endarterectomy, stroke, cerebral hemorrhage), bacterial meningitis, end-stage renal disease and all non-AIDS defining malignancies

Subjects were followed from first CMV available test (baseline) to first event/last observation/first negative HCV-RNA. Four separate Cox regression models were fitted and adjusted for the following covariates at baseline: gender, age, mode of HIV transmission, nadir CD4, CD4 and HIVRNA, alcohol consumption, number of co-morbidity, ARV exposure, CDC C stage, Fib4 index and calendar year of baseline

RESULTS

9479 patients had known baseline CMV IgG serostatus, of these 2288 (24%) were HCV-Ab positive and included in the analysis; 1882 (82%) were HIV/CMV/HCV coinfected, while 406 (18%) were HIV+/CMV-/HCV+. Baseline characteristics were assessed at the time of enrollment, only 11% of patients are on cART at enrollment, whereas all patients started subsequently. CD8 count (median 820 in CMV- vs 902 in CMV+, p=0.001) was higher in CMV positive. No differences were observed for liver related parameters (AST, ALT, Fib-4, APRI) (table 1). Then we considered only viremic patients for HCV and 997 pts were found to have detectable HCV-RNA (table 2).

Cumulative proportion of patients experiencing the composite end-point: first event between ESLD and Fib4>3.25 was estimated by Kaplan Meier method on all the study population (N=2288) and it is shown in fig. 1.

Adjusted hazard risk estimated by Cox regression model of 4 different outcomes (1.ESLD, 2.ESLD+fib4>3.25, 3.AIDS/death for AIDS event, 4. non AIDS event) according to CMV IGg status in all study population and in the subgroup of HCV-RNA positive pts are shown in fig. 2. Multivariable models on the total study population showed that CMV negative subjects seemed to have reduced, but not significant risk of all outcomes.

Table 1. Demographics and clinical characteristics of HCV-Ab+ subjects : CMV+ and CMV-

	N=406 CMV-		N=1882 CMV+		p-value
	n	%	n	%	
Gender					
male	308	75.9%	1377	73.2%	0.264
female	98	24.1%	505	26.8%	
Age, median (IQR)	36	33-40	37	33-41	0.106
Mode of HIV transmission					
heterosexual	57	14.0%	228	12.1%	0.252
IVDU	321	79.1%	1472	78.2%	
homosexual	19	4.7%	133	7.1%	
Other/unknown	9	2.2%	49	2.6%	
Migrants	14	4.4%	112	6.0%	0.231
CDC stage C	53	13.1%	198	10.5%	0.138
Nadir CD4>=200 at BL	284	70.0%	1423	75.6%	0.007
CD4 at BL					
<350	171	42.1%	715	38.0%	0.234
350-500	77	19.0%	429	22.8%	
500+	156	38.4%	733	39.0%	
missing	2	0.5%	5	0.3%	
CD4 at BL, median (IQR)	408	197-608	430	250-621	0.119
CD8 at BL, median (IQR)	820	543-1172	902	630-1230	0.001
CD4/CD8 ratio, median (IQR)	0.46	0.27-0.72	0.45	0.26-0.69	0.362
HIVRNA, log 10 copies/mL, at BL					
<5 log	302	74.4%	1422	75.6%	0.313
>=5 log	93	22.9%	386	20.5%	
missing	11	2.7%	74	3.9%	
Alchool use					
absteiners	77	19.0%	386	20.5%	0.295
occasional use	20	4.9%	101	5.4%	
daily use	26	6.4%	165	8.8%	
missing	283	69.7%	1230	65.4%	
# comorbidiies					
0	394	97.0%	1819	96.7%	0.431
1	9	2.2%	57	3.0%	
2	3	0.8%	6	0.3%	
Years of BL					
1997-2001	305	75.1%	1288	68.4%	0.048
2002-2006	46	11.3%	243	12.9%	
2007-2011	23	5.7%	159	8.5%	
2012-2017	32	7.9%	192	10.2%	
FIB 4, median (IQR)	1.40	0.93-2.23	1.39	0.93-2.38	0.633
APRI, median (IQR)	0.67	0.41-1.18	0.65	0.36-1.30	0.586
ALT, median (IQR)	50	31-81	45	27-79	0.085
AST, median (IQR)	45	30-70	42	28-73	0.320

Table 2. Demographics and clinical characteristics of HCV viremic subjects: CMV+ and CMV -

	N=188 CMV-		N=809 CMV+		p-value
	n	%	n	%	
Gender					
male	137	72.9%	584	72.2%	0.850
female	51	27.1%	225	27.8%	
Age, median (IQR)	37	34-40	37	34-42	0.224
Mode of HIV transmission					
heterosexual	32	17.0%	90	11.1%	0.021
IVDU	143	76.1%	623	77.0%	
homosexual	6	3.2%	67	8.3%	
Other/unknown	7	3.7%	29	3.6%	
Migrants	8	4.3%	52	6.4%	0.259
CDC stage C	20	10.6%	79	9.8%	0.718
Nadir CD4>=200 at BL	139	73.9%	617	76.3%	0.501
CD4 at BL					
<350	66	35.1%	314	38.8%	0.561
350-500	40	21.3%	176	21.8%	
500+	82	43.6%	316	39.1%	
missing	0	0.0%	3	0.4%	
CD4 at BL, median (IQR)	459	232-655	428	266-617	0.528
CD8 at BL, median (IQR)	894	574-1172	923	653-1258	0.074
CD4/CD8 ratio, median (IQR)	0.5	0.31-0.75	0.45	0.25-0.68	0.068
HIVRNA, log 10 copies/mL, at BL					
<5 log	143	76.1%	614	75.9%	0.801
>=5 log	39	20.7%	161	19.9%	
missing	6	3.2%	34	4.2%	
Alchool use					
absteiners	52	27.7%	200	24.7%	0.295
occasional use	8	4.3%	63	7.8%	
daily use	15	8.0%	77	9.5%	
missing	113	60.1%	469	58.0%	
# comorbidiies					
0	181	96.3%	782	96.7%	0.720
1	7	3.7%	25	3.1%	
2	0	0.0%	2	0.2%	
Years of BL					
1997-2001	127	67.6%	470	58.1%	0.090
2002-2006	25	13.3%	133	16.4%	
2007-2011	14	7.5%	98	12.1%	
2012-2017	22	11.7%	108	13.4%	
FIB 4, median (IQR)	1.44	0.97-2.27	1.47	0.96-2.43	0.662
APRI, median (IQR)	0.7	0.43-1.13	0.73	0.41-1.34	0.771
ALT, median (IQR)	52	35-82	52	34-84	0.952
AST, median (IQR)	45	31-68	47	32-77	0.621
HCVRNA, log10 median (IQR)	5.9	5.4-6.3	5.9	5.5-6.4	0.178

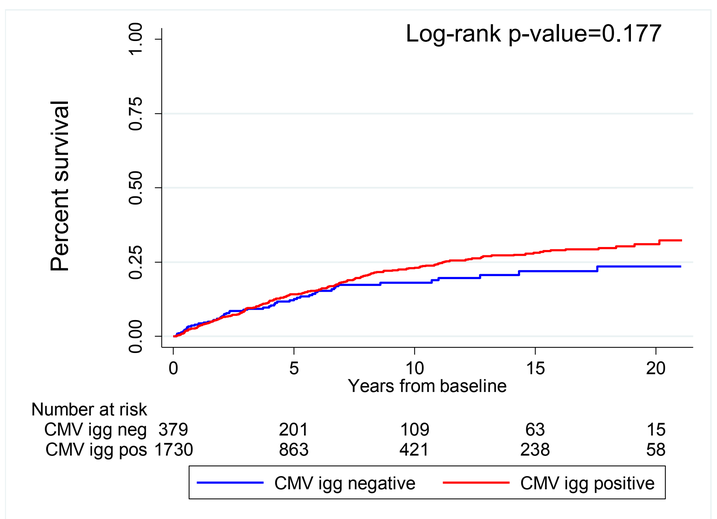

Figure 1. Cumulative proportion of patients experiencing composite end-point: first between ESLD and Fib4>3.25

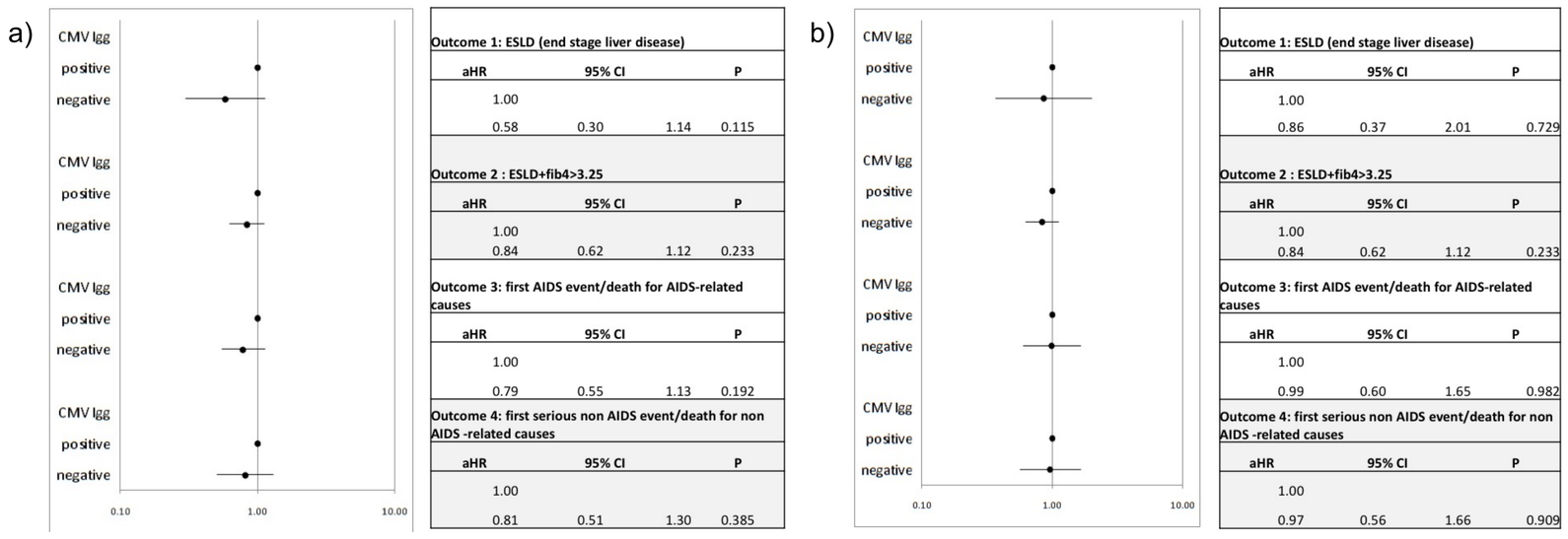

Figure 2. Adjusted hazard risk estimated by Cox regression model of 4 different outcomes (1.ESLD, 2. ESLD +fib4>3.25, 3. AIDS/death for AIDS event, 4. non AIDS event) according to CMV IGg status in all study population (a) and in HCV-RNA positive pts (b)

CONCLUSIONS

In our study population of CMV/HCV/HIV coinfected subjects, CD8+ cell count is higher confirming a driving role of CMV in CD8 expansion. In the whole population, multivariable models showed that CMV-seronegative subjects had a non-significantly lower risk of all studied outcomes, probably due to the limited number of events or the predominant effect of HCV infection. Further analysis is needed to understand the effect of CMV coinfection in this specific population, particularly in the perspective of HCV eradication.

Acknowledgments

ICONA Foundation Study Group

BOARD OF DIRECTORS: *A d'Arminio Monforte (President), A Antinori (Vice-President), M Andreoni, A Castagna, F Castelli, R Cauda, G Di Perri, M Galli, R Iardino, G Ippolito, A Lazzarin, GC Marchetti, G Rezza, F von Schloesser, P Viale.*

SCIENTIFIC SECRETARY: *A d'Arminio Monforte, A Antinori, A Castagna, F Ceccherini-Silberstein, A Cozzi-Lepri, E Girardi, S Lo Caputo, C Mussini, M Puoti, CF Perno.*

STEERING COMMITTEE: *A Antinori, F Bai, C Balotta, A Bandera, S Bonora, M Borderi, A Calcagno, A Capetti, MR Capobianchi, A Castagna, F Ceccherini-Silberstein, S Cicalini, A Cingolani, P Cinque, A Cozzi-Lepri, A d'Arminio Monforte, A De Luca, A Di Biagio, E Girardi, N Gianotti, A Gori, G Guaraldi, G Lapadula, M Lichtner, S Lo Caputo, G Madeddu, F Maggiolo, G Marchetti, L Monno, C Mussini, S Nozza, CF Perno, C Pinnetti, M Puoti, E Quiros Roldan, R Rossotti, S Rusconi, MM Santoro, A Saracino, L Sarmati.*

STATISTICAL AND MONITORING TEAM: *A Cozzi-Lepri, I Fanti, L Galli, P Lorenzini, A Rodano', M Macchia, A Tavelli.*

BIOLOGICAL BANK INMI: *F Carletti, S Carrara, A Di Caro, S Graziano, F Petroni, G Prota, S Truffa.*

PARTICIPATING PHYSICIANS AND CENTERS: *Italy A Giacometti, A Costantini, V Barocci (Ancona); G Angarano, L Monno, C Fabrizio (Bari); F Maggiolo, C Suardi (Bergamo); P Viale, V Donati, G Verucchi (Bologna); F Castelnuovo, C Minardi, E Quiros Roldan (Brescia); B Menzaghi, C Abeli (Busto Arsizio); B Cacopardo, B Celesia (Catania); J Vecchiet, K Falasca (Chieti); A Pan, S Lorenzotti (Cremona); L Sighinolfi, D Segala (Ferrara); P Blanc, F Vichi (Firenze); G Cassola, C Viscoli, A Alessandrini, N Bobbio, G Mazzarello (Genova); M Lichtner, S Vita, (Latina); P Bonfanti, C Molteni (Lecco); A Chiodera, P Milini (Macerata); G Nunnari, G Pellicanò (Messina); A d'Arminio Monforte, M Galli, A Lazzarin, G Rizzardini, M Puoti, A Castagna, S Cannizzo, MC Moioli, R Piolini, AL Ridolfo, S Salpietro, C Tincati, (Milano); C Mussini, C Puzzolante (Modena); C Migliorino, G Lapadula (Monza); V Sangiovanni, G Borgia, V Esposito, F Di Martino, I Gentile, L Maddaloni (Napoli); AM Cattelan, S Marinello (Padova); A Cascio, C Colomba (Palermo); F Baldelli, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); G Magnani, MA Ursitti (Reggio Emilia); M Andreoni, A Antinori, R Cauda, A Cristaudo, V Vullo, R Acinapura, G Baldin, M Capozzi, A Mondi, A Cingolani, M Rivano Capparucia, G Iaiani, A Latini, R Gagliardini, MM Plazzi, S Savinelli, A Vergori (Roma); M Cecchetto, F Viviani (Rovigo); G Madeddu, P Bagella (Sassari); A De Luca, B Rossetti (Siena); A Franco, R Fontana Del Vecchio (Siracusa); D Francisci, C Di Giuli (Terni); P Caramello, G Di Perri, S Bonora, GC Orofino, M Sciandra (Torino); M Bassetti, A Londero (Udine); G Pellizzer, V Manfrin (Vicenza); G Starnini, A Ialungo (Viterbo).*

References

1. Lichtner M et al. for the Icona Foundation Study. HIV and CMV co-infection is associated with increased risk of non AIDS events in a large cohort of HIV-infected patients. JID 2015.
2. Hsue PY et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. AIDS 2006.
3. Kuniholm MH et al. Hepatitis C viremia is associated with cytomegalovirus IgG antibody levels in HIV-infected women. PlosOne, 2013.

Funding

ICONA Foundation is supported by unrestricted grants from Gilead, Janssen, MSD and ViiV Healthcare.