HLA-B18 as a risk factor of progression to severe liver fibrosis in HIV/HCV patients

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Background & aims

Chronic infection by hepatitis C virus (HCV) is characterized by progressive liver fibrosis. Although several factors have been found to be associated with faster liver fibrosis progression, a biomarker with sufficient predictive value to impact clinical decision making has not been identified. The aim of our study was to analyze the influence of HLA-B molecules on liver fibrosis progression in HIV/HCV patients without cirrhosis.

Methods

A retrospective longitudinal study included HIV/HCV patients in follow-up between 2007 and 2014.

Patients who met the following inclusion criteria constituted the study population:
a) active HCV-infection at baseline and during follow-up (defined as detectable RNA-HCV viral load in peripheral blood)
b) naïve to HCV treatment or patients who did not achieve a sustained viral response (SVR)
c) at least two determinations of Liver Stiffness Measurement (LSM)
d) Non cirrhosis at baseline, defined as an LSM≥14.6 kPa. Analytical, demographic and clinical variables were collected.

LSM cutoffs applied were: <6.5 kPa (F0-F1); 6.5-9.4 kPa (F2); 9.5-14.5 kPa (F3) and ≥14.6 kPa (F4). The variables collected were age, sex, baseline CD4+ cell count (cells/mL), HCV genotype, HCV and HIV viral load, LS (kPa), HLA-B genotyping, use of antiretroviral therapy (ART) and acquire immunodeficiency syndrome (AIDS) condition.

Outcome variables were: 1) fibrosis stage progressed at least one stage; and 2) fibrosis progressed up to severe liver fibrosis (F3-F4). Patients were censored at: a) an event of interest; b) loss of follow-up; and d) end date of study.

Survival analysis was use to identify variables associated with liver fibrosis progression. The analysis was performed in: i) the overall population, ii) HCV-treatment naïve patients, iii) Treatment experienced patients.
Multivariate survival analysis was conducted using Cox's regression model

Results

One-hundred and fifty-six patients constituted the study population (**Table 1**). The patient distribution according to liver fibrosis was as follows: F0-F1, 84 (53.8%) patients; F2, 36 (26.1%) patients; and F3, 36 (26.1%) patients. The median (IQR) follow-up period for these patients was 62 (IQR: 29-78) months. Sixty-six patients (42.3%) showed an increase in the degree of fibrosis (time to event: 29 [IQR: 14-49.5] months).

Table 1 Baseline characteristics

Clinical characteristic	Condition	N = 156
Age (years), median (IQR)		49 (45-53)
Sex, no (%)	Male	130 (83.3)
	Female	26 (16.7)
CD4+ cellscount (cells/mL), median (IQR)		471 (320-665)
HIV viral load, no (%)	Undetectable	117 (75)
	Detectable	39 (25)
AIDS-definingcriteria, no (%)	Yes	51 (32.7)
	No	105 (67.3)
HCV-genotype, no (%)	1	102 (65.4)
	2	3 (1.9)
	3	22 (14.4)
	4	26 (16.7)
	Unknow	3 (1.9)
HCV viral load (log IU/mL), median (IQR)		6.2 (5.4-6.6)
Liver fibrosis stage, no(%)	F0-F1	84 (53.8)
	F2	36 (23.1)
	F3	36 (23.1)

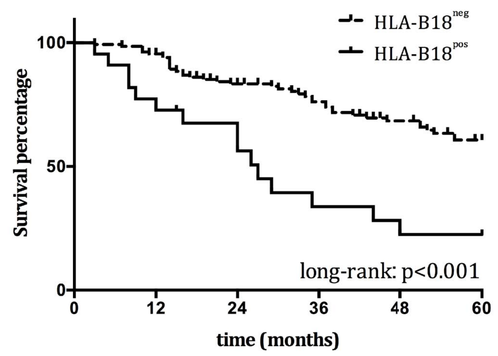
Table 2 shows the bivariate analysis of factors potentially associated with liver fibrosis progression. Patients bearing HLA-B18 more frequently had liver fibrosis and had a faster liver fibrosis progression rate (72.7%; time to event 24 [IQR: 8.2-33.5] months) than HLA-B18neg patients (38.2%; time to event 33.5 [IQR: 14-52.2] months).

Table 2 Univariate analysis for liver fibrosis progression

Clinical characteristic	Condition	Subjectwithprogression	Long Rank
Age (years)	< 45	14 (42.4)	0.747
	≥45	52 (42.3)	
Sex	Male	59 (25.4)	0.352
	Female	7 (26.9)	
CD4+ cellscount (cells/mL)	< 350	17 (36.2)	0.471
	≥ 350	48 (44.9)	
HIV viral load	Undetectable	46 (39.3)	0.228
	Detectable	20 (52.6)	
AIDS-definingcriteria	Yes	22 (43.1)	0.76
	No	43 (41.7)	
HCV-genotype	1	39 (38.2)	0.671
	2	0	
	3	10 (45.5)	
	4	16 (61.5)	
HCV viral load (log IU/mL)	< 600,000	18 (40.9)	0.763
	≥ 600,000	47 (43.5)	
Liver fibrosis stage	F0-F1	33 (39.3)	0.126
	F2	20 (55.6)	
	F3	13 (36.1)	
HLA-B genotype	F2		36 (23.1)
B-07	Positive	8 (33.3)	0.487
	Negative	58 (43.9)	
B-14	Positive	12 (36.4)	0.233
	Negative	54 (43.9)	
B-18	Positive	16 (72.7)	< 0.001
	Negative	50 (37.3)	
B-35	Positive	10 (34.5)	0.336
	Negative	56 (44.1)	
B-40	Positive	10 (58.8)	0.187
	Negative	56 (40.3)	
B-44	Positive	15 (35.7)	0.329
	Negative	51 (44.7)	

The survival analysis (**Figure 1**) showed that the probability of developing an increase in liver fibrosis of at least one stage was higher in HLA-B18pos patients than in HLA-B18neg patients during the follow-up period.

Figure 1



Similar results were found when the analysis was performed separately for patients naïve to treatment (**Figure 2A**) and patients treated who did not achieve sustained virological response (**Figure 2B**).

Figure 2A

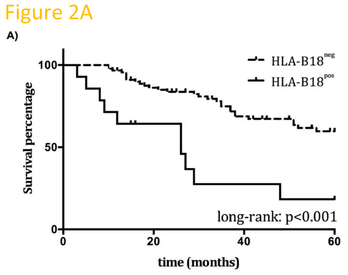
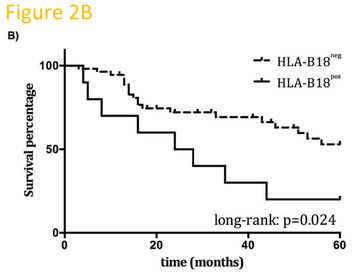


Figure 2B



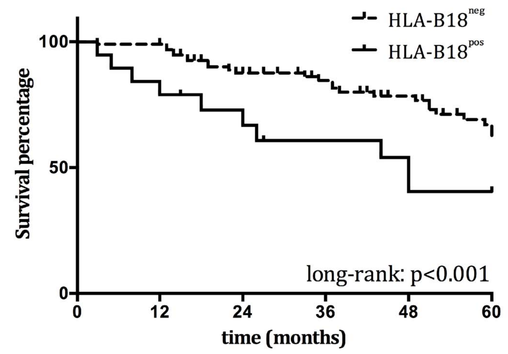
By multivariate Cox regression analysis, presence of HLA-B18 and was identified as the only independent risk factors of liver fibrosis progression after adjustment for other clinical variables (**Table 3**).

Table 3 Multivariate analysis for liver fibrosis progression

Clinical characteristic	Condition	Adjust HR (95% CI)	p
Age (years)	< 45	0.95 (0.51-1.78)	0.891
	≥45	1	
Sex	Male	0.91 (0.4-2.08)	0.837
	Female	1	
HIV viral load	Undetectable	0.6 (0.34-.1.05)	0.076
	Detectable	1	
AIDS-definingcriteria	Yes	1.43 (0.82-2.49)	0.207
	No	1	
HCV viral load (log IU/mL)	< 600,000	1	0.32
	≥ 600,000	1.33 (0.75-2.37)	
HLA-B18 genotype	Positive	3.82 (2.06-7.1)	< 0.001
	Negative	1	

Among patients with baseline liver fibrosis of F0-F2 stage, those who were HLA-B18pos more frequently experienced liver fibrosis progression to F3-F4 than those who were HLA-B18neg (13/19: 68.4% vs. 30/101: 29.7%; p=0.003). The median time to event in HLA-B18pos and HLA-B18neg patients was 26 (IQR: 10-64) months and 37 (IQR: 17.5-57.5) months, respectively. The survival analysis showed that the probability of F0-F2 patients progressing to advanced or severe fibrosis (F3-F4) was higher in HLA-B18pos patients than in HLA-B18neg patients during the follow-up period (**Figure 3A**).

Figure 3



Moreover, the patients who were naive to HCV treatment had a time to event of 18 (IQR: 6.5-37) months and 37 (IQR: 19-52) months for HLA-B18pos and HLA-B18neg, respectively (**Figure 4A**). However no differences were found between patients who did not achieve SVR (**Figure 4B**).

Figure 4A

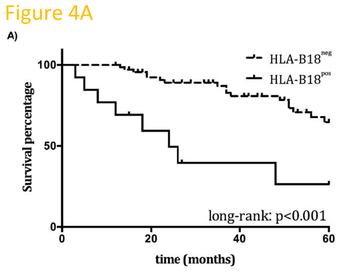
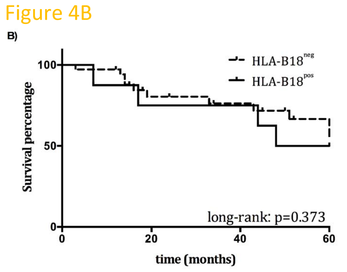


Figure 4B



Conclusions

HIV/HCV patients non-cirrhotic carrying allele HLA-B18 were more likely to progress more rapidly to developing advanced and severe fibrosis (F3-F4) than HLA-B18neg patients. These results could help make decisions about the timing of HCV therapy in HLA-B18pos patients with absent or mild fibrosis.

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