

Histological Findings, Predictors of Severe Fibrosis, and Assessment of Factors with Impact on the Fibrosis Progression Rate in HIV-infected Patients with Chronic Hepatitis C in the Era of HAART

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BACKGROUND

There is controversy on predictors of histological severity and the role of HAART on the fibrosis progression rate (FPR) in HIV/HCV co-infection.

METHODS

Prospective, non-randomized study of 323 consecutive, HBVsAg (-), caucasian, HCV-treatment naive, HIV-infected patients with chronic hepatitis C undergoing liver biopsy (LB) between January 1998-May 2007.

Objectives

- To describe histological findings and to assess, using univariate and multivariate regression analyses, baseline predictors of histological severity (F_{≥3}).
- To assess, using univariate and multivariate regression analyses, baseline factors influencing FPR (cutoff >0.1) in 302 subjects with known date of HCV infection acquisition (93% of the population).

RESULTS Baseline HIV features and HAART

Age (years; mean ± SD)	40±5
Male Sex (n, %)	241 (75%)
Prior IVDU (n, %)	280 (87%)
Prior AIDS (n, %)	100 (31%)
Baseline CD4 count (cells/ml; median, range)	484 (1-1512)
- Nadir CD4 count (cells/ml; median, range)	177 (2-888)
- Prior counts <200 cells/ml (n, %)	188 (58%)
Baseline HIV-load (log ₁₀ copies/ml; median, range)	1.7 (1.7-5.7)
- VL <1.7log ₁₀ copies (n, %)	207 (64%)

At liver biopsy

No HAART	44 (14%)
HAART	279 (86%)
- PI-based (n, %)	112 (35%)
- NNRTI (n, %)	111 (34%)
- 3 NRTI (n, %)	43 (13%)
- 2 NRTI (n, %)	7 (2%)
- Mixed families (n, %)	6 (2%)
Prior HAART history	
No HAART	37 (11%)
HAART	286 (89%)
- Only PI-based (n, %)	90 (28%)
- Only NNRTI (n, %)	31 (10%)
- Both PI&NNRTI (n, %)	165 (51%)
Median exposure to drugs (months, range)	
- PI	34 (1-108)
- NNRTI	18 (1-92)

Baseline HCV features

Time of HCV infection (years; median, range)	20 (3-31)
HCV genotype (n, %)	
- 1 or 4	254 (80%)
- 2 or 3	69 (20%)

Liver biopsy results

-HAI (median, range)	6 (0-12)
-Fibrosis scoring (median, range and (n, %))	
- 0	2 (0-4)
- 1	29 (9%)
- 2	121 (38%)
- 3	61 (19%)
- 4	69 (21%)
- 5	43 (13%)

HCV-RNA (log ₁₀ IU/ml; median, range)	6.0 (2.0-6.85)
->800,000 IU/ml	(59%)
AST (U/l; median, range)	56 (12-909)
ALT (U/l; median, range)	75 (11-578)
GGT (U/l; median, range)	141 (12-2076)
-GGT≥100 U/l	201 (62%)
Alkaline phosphatase (U/l; median, range)	100 (36-4388)
Albumin (g/dl; median, range)	4.5 (2.6-6.0)
Prothrombin activity (%; median, range)	94 (44-126)
Platelet count (cells/ml; median, range)	163x10 ³ (13.2-431)

Estimated median FPR 0.09 units/year [IQR 0.05-0.15]; FPR>0.1 128 (42%)

Univariate analysis of factors associated to Severe Fibrosis (F_{≥3})

	Severe fibrosis (n=112, 34%)	Non-Severe Fibrosis (n=210, 66%)	P
Age (years, mean±SD)	41±4.4	39±5.2	0.06
Prior IVDU (n, %)	102 (91%)	178 (84%)	0.091
Time of HCV (years, mean±SD)	20±4.6	19±5.0	0.09
PI exposure (n, %)	94 (84%)	161 (76%)	0.11
Months on PI (mean±SD)	32±26	27±25	0.074
NNRTI exposure (n, %)	69 (62%)	127 (60%)	0.80
Months on NNRTI (mean±SD)	12±15	16±21	0.47
GGT ≥ 100 U/l (n, %)	81 (72%)	120 (57%)	0.007*
Prior CD4 counts <200 cells/ml	74 (66%)	114 (54%)	0.037*
CD4 at LB (cells/ml; mean±SD)	459±273	552±283	0.001*

Additional factors associated to severe fibrosis at LB: prothrombin activity (p=0.0001*), albumin (p=0.0001*), bilirubin (p=0.0001*), AST (p=0.0001*), ALT (p=0.03*), GGT (p=0.021*), alkaline phosphatase (p=0.0001*), and platelet count (p=0.001*)

HCV-genotype and HCV-RNA levels were not significantly associated to severe fibrosis

Multivariate regression analysis of factors associated to Severe Fibrosis (F_{≥3})

	OR	95% CI	P
Age (years)	1.075	1.022-1.131	0.005*
Prior IVDU	2.316	1.037-5.170	0.04*
GGT ≥ 100 U/l	2.057	1.232-3.436	0.006*
Baseline CD4 counts	0.999	0.998-1	0.004*

CONCLUSIONS

- In our HIV/HCV-cohort, LB showed severe fibrosis (F_{≥3}) in 34% of subjects.
- Older age, prior IVDU and, at LB, GGT values ≥100 U/l and/or lower CD4 counts predicted severe fibrosis.
- Neither exposure to or time on PI/NNRTI significantly affected histological severity, but PI exposure and GGT values at LB ≥100 U/l were associated to a higher fibrosis progression rate.
- In patients with PI exposure, there was a significantly higher frequency of factors predicting histological severity, such as older age, prior severe immunosuppression, and AIDS diagnosis.

Univariate and multivariate analyses of factors associated to FPR >0.1 units/year**

	FPR>0.1 units/y (n=128, 42%)	FPR<0.1 units/y (n=174, 58%)	P
Prior IVDU (n, %)	118 (92%)	159 (91%)	0.80
Time of HCV (years, mean±SD)	20±4.6	19±5.0	0.09
HAART-naïve (n, %)	117 (91%)	149 (86%)	0.12
Months on PI (mean±SD)	30±25	27±25	0.17
NNRTI exposure (n, %)	80 (62.5%)	106 (61%)	0.78
Months on NNRTI (mean±SD)	12±14	17±22	0.34
GGT ≥ 100 U/l (n, %)	90 (70%)	99 (57%)	0.02*
PI exposure (n, %)	108 (84%)	129 (74%)	0.032*
CD4 at LB (cells/ml; mean±SD)	479±275	540±280	0.03*

	OR	95% CI	P
Exposure to PI	1.861	1.031-3.359	0.039*
GGT ≥ 100 U/l	1.743	1.070-2.838	0.026*

** In patients with known date of HCV acquisition (n=302)

Comparative analysis of baseline features according to PI exposure

	PI exposure (n=237, 78%)	No-PI exposure (n=65, 22%)	P
Age (years; mean±SD)	40 ± 4.7	39 ± 4.8	0.03*
Male sex (n, %)	178 (75%)	48 (74%)	0.83
Prior AIDS (n, %)	85 (36%)	9 (14%)	0.001*
CD4 count at LB (cells/ml; mean±SD)	520 ± 291	494 ± 232	0.86
-Nadir CD4 count (cells/ml; mean±SD)	175 ± 144	301 ± 174	0.0001*
-Prior counts <200 cells/ml (n, %)	156 (66%)	17 (26%)	0.0001*
HCV-RNA level >800,000 IU/ml (n, %)	108 (56%)	33 (62%)	0.43
Years of HCV infection (mean±SD)	19 ± 5	19 ± 4.7	0.48