Severity of liver disease associated with IL-10 DNA Polymorphisms in patients coinfected with HIV and HCV

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Background

- The relationship of the immune responses to liver injury in HCV and HIV is poorly understood but may be important in understanding
  - the pathogenesis of liver damage
  - improving treatment outcomes
- Interleukin (IL) 10 is thought to modulate protective immune responses
- IL-10 may have an important pathogenic role in HCV outcomes

Aim

- To assess the association between histologic severity of liver disease in HIV and HCV co-infected individuals and
  - allelic variation in IL-10
  - IL-10 secretion in response to HCV proteins

Patients and ACTG 5071

- ACTG 5071- randomized trial to determine the efficacy of HCV therapy in HCV/HIV co-infection
- 134 subjects
- Liver biopsy within 48 weeks of study entry.
- DNA from 81 A5071 subjects who consented to human genetic analysis
- Single Nucleotide Polymorphism (SNP) analyses reported as wild type (wt), variant (v), heterozygous (wt/v) for
  - IL-10, IL-1α, and Complement factor 5 (C5)

Demographic of subjects

- Demographics and response to therapy of 81 HIV and HCV co-infected subjects who consented did not differ from parent study
  - except more subjects >40 y consented to DNA analysis
- Receipt of pegylated IFN associated with
  - 24 week response ($p<0.001$) to treatment
  - Sustained Virologic Response ($p<0.03$)

	All patients (n=81)	Interferon and Ribavirin (n=38)	Peginterferon and Ribavirin (n=43)	p-value
Male gender	63 (78%)	30 (79%)	33 (77%)	0.81
Race or ethnic group White Non-Hispanic Black Non-Hispanic Hispanic Other	40 (49%) 23 (28%) 15 (19%) 3 (4%)	16 (42%) 12 (32%) 8 (21%) 2 (5%)	24 (56%) 11 (26%) 7 (16%) 1 (2%)	0.64
Age (years)*	45 (36-60)	44.5 (36-55)	45 (36-60)	ns
Karnofsky score 80 90 100	10 (12%) 42 (52%) 26 (32%)	6 (16%) 20 (53%) 9 (24%)	4 (9%) 22 (51%) 17 (40%)	0.36
Baseline CD4*	463.5 (85-1376)	438.8 (85-1001)	481 (169.5-1376)	ns
Baseline HIV-1 RNA <50 copies/mL	46 (57%)	23 (61%)	23 (53%)	0.52
Receiving protease inhibitors	44 (54%)	26 (68%)	18 (42%)	0.02
Log_{10} HCV RNA IU/mL	6.28 (4.32-6.83)	6.25 (5.19-6.55)	6.30 (4.32-6.83)	ns
HCV genotype 1	61 (75%)	29 (76%)	32 (74%)	0.84
Abnormal ALT at baseline	57 (70%)	27 (71%)	30 (70%)	0.90
HAI A-D at entry*	5 (1-10)	4.5 (1-10)	5 (2-8)	0.71
HAI-E at entry 0-2 3-6	48 (59%) 33 (41%)	25 (66%) 13 (34%)	23 (53%) 20 (47%)	0.26
24 week Virologic Response (VR)	28 (35%)	4 (11%)	24 (56%)	<.0001
Sustained Virologic Response (SVR)	18(22%)	4(11%)	14 (33%)	0.03

*median (range)
Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; HAI, hepatic activity index

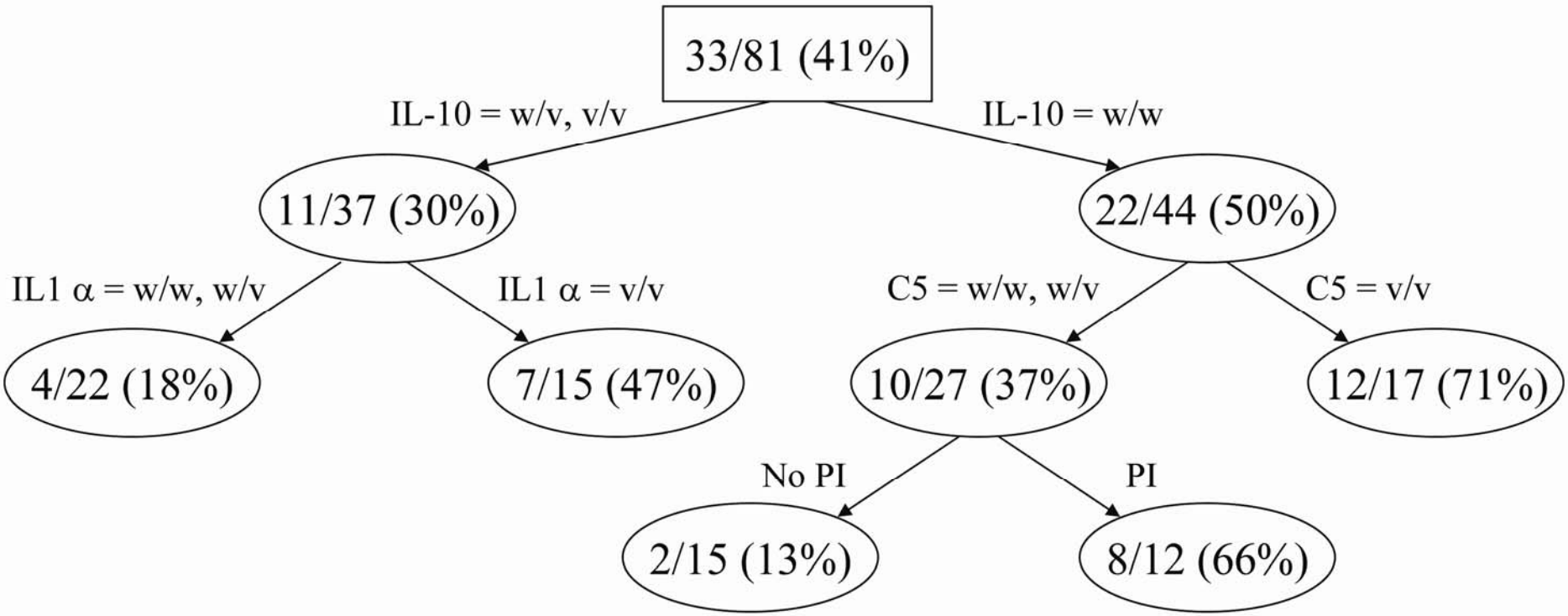
Methods and Statistics

ELISPOT assays

- Performed on PBMC for IL-10 using HCV antigens core, NS3 and NS5.
- Averaged numbers of spot-forming cells (SFC) in control wells were subtracted from stimulated wells to correct for spontaneous cytokine production and reported as SFC/million PBMC.

Data were analyzed using nonparametric methods. Recursive partitioning (CART) was employed to identify predictors of fibrosis (HAI-E score)

CART Factors Predicting High Baseline HAI-E Score (3-6)



Advanced Liver Fibrosis associated with wt IL-10 and variant C5 alleles

Advanced fibrosis (HAI-E score 3-6) noted in

- 33/81 (41%) of all ACTG 5071 subjects
- 71% of those with wt IL-10 alleles and variant C5 alleles

- compared with 18% among those who had variant IL-10 and wt IL-1 α alleles.

IL-10 production by PBMC

Assessed by ELISpot in 107 of 134 subjects treated in ACTG A5071study

Virologic responders to therapy seen in those with

- higher baseline IL-10 production
- decreased production at week 24 compared to baseline

  {Graham, Wells, et al. 2006**}**

59 subjects had both baseline IL-10 production and DNA polymorphisms performed

- Those with wild type IL-10 had a trend towards lower IL-10 production (p=0.27)

IL-10 secretion in response to HCV proteins

ELISPOT Antigen	wt/wt compared to wt/v & v/v p value
• HCV ns3	0.27
• HCV core	0.33
• candida	0.59
• HCV ns5	0.86

Kruskall-Wallis P-value

Conclusions

- Allelic variations in IL-10, C5 and IL-1α are associated with severity of chronic HCV disease
- These proteins are critical to the inflammatory response
- Further studies should address whether allelic variations in IL-10 alter production of IL-10 and investigate the association of IL-10 with severity of liver fibrosis