



Selected abstracts on HIV and Hepatitis Coinfection from the 11th Conference on Retroviruses and Opportunistic Infections (CROI) held in San Francisco, CA on February 8-11, 2004.

Neuropathogenic Manifestations of HIV Infection

Abstract 26

Hepatitis C and Neuropsychological Function In Treatment Naive HIV-1-infected Subjects - A5097s Baseline Analysis

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Background

HIV-1 and HCV cause neurologic complications but it is unclear whether HIV and HCV interact. We evaluate the effect of HCV/HIV co-infection on neuropsychological performance and depression in ARV- and anti-HCV treatment-naïve subjects.

Methods

A5097s is a substudy of A5095, a phase 3 antiretroviral treatment protocol for treatment-naïve HIV-infected subjects. We evaluated the populations at baseline before any therapy was initiated. Neuropsychological performance tests included Trailmaking Test (parts A and B) and the Digit Symbol task, which together assess attention, speed of information processing, and mental flexibility. Depression was assessed with the Center for Epidemiologic Studies-Depression Scale (CES-D). HCV status was determined by the presence of anti-HCV antibody at entry. For each subject, a baseline z-score was calculated for each subtest, representing the number of standard deviations away from an age-adjusted normative performance. The results were compared between the HCV/HIV-co-infected and the HIV-infected only groups.

Results

Of patients enrolled in A5097s, 235 had HCV status data available at entry (25 HCV+ and 210 HCV-). The HCV+ and HCV- groups were comparable except that the HCV+ group had higher prevalence of history of IV drug use and lower educational level ($p < 0.05$). The HCV+ group had significantly lower Z-scores in neuropsychological performance overall, (0.69 vs 0.13 SDs below the mean, $p = 0.012$). Among 3 subtests, the HCV+ group performed less well than the HCV- group on the Digit Symbol task, (0.92 vs 0.21 SDs below the mean, $p < 0.001$). Multivariate modeling suggests that there is a significant relationship between HCV-infection status and performance in the Digit Symbol task even when controlling for confounding variables (education, sex, IV drug use, CD4 count, HIV-1 RNA, depression, alcohol use, and hepatitis B status). Of the HCV+ subjects 52% and of HCV- subjects 33% had significant

depression ($p=0.055$). Group differences resulted from significantly higher scores on the “somatic complaint” portion of the CES-D scale ($p<0.001$).

Conclusions

Our findings suggest that HCV/HIV co-infection adversely affected neuropsychological performance, particularly in the Digit Symbol task. HCV may also be associated with depressed mood particularly with somatic complaint. Despite a limited sample size and the difficulty of excluding all possible confounding factors, our results control for many potential confounds while still demonstrating a probable effect of hepatitis C on neuropsychological performance.

Abstract 27

Risk Factors and Determinants for HIV-associated Sensory Neuropathies: Is Hepatitis C a Modifier?

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Background

Specific NRTI (ddI, d4T, and ddC) inhibit mitochondrial DNA polymerase γ and provoke symptomatic HIV-associated sensory neuropathies (HIV-SN). Risk factors include age, higher viral set-point, and lower CD4 count, however, the modifier role of hepatitis C is uncertain.

Methods

We assessed 130 HIV-infected adults by: Case IV quantitative sensory testing, skin biopsies and assays for hepatitis C, vitamin B12, hemoglobin A1C, and plasma lactate. The 2 sites (JHU and MU) were selected to provide contrasting demographics and hepatitis C seroprevalence. ART assessments included cumulative exposure to neurotoxic RTI (ntx-DDX). Epidermal innervation was assessed using PGP9.5 immunostaining. mtDNA was quantified in subcutaneous fat using real-time PCR.

Results

At JHU, of 47 subjects, 78% were male, 83% black, 70% had a history of IDU, mean CD4 count was 289, and hepatitis C seroprevalence was 71%. At MU, of 83 subjects, 95% were white, 96% male, 92% had a history of MSM, mean CD count was 356, and hepatitis C seroprevalence was 11%. At baseline, HAART was used in 79% at JHU, and 90% at MU. Ntx-DDx agents were used in 21% at JHU, and 53% at MU, with ddI and d4T used together in combination in 4% and 15%, respectively. The distribution of subjects was (JHU/MU): neuropathy-free 30%/36%; asymptomatic SN (asx-SN) 17%/7%; and symptomatic SN (sx-SN) 52%/56%, with no inter-center differences. Thermal and vibration thresholds were measured with the Case IV device and were abnormal in 26% of those with asx-SN, and 45% with sx-SN. From 62 completed biopsies in 31 subjects at JHU, morphology was concordant with SN status in 61%, and 50% of neuropathy-free subjects had morphological abnormalities. Neither age, CD4 counts, plasma lactate, B12 levels, mtDNA in SC fat, nor hepatitis C serology were associated with symptomatic SN at baseline.

Conclusions

The frequency of asymptomatic and symptomatic sensory neuropathies was remarkably high at both sites, with only 32% of subjects neuropathy-free at baseline. Hepatitis C serostatus did not appear to influence the prevalence of SN at baseline, however, longitudinal study will disclose its modifier role. Morphological abnormalities were noted in a high proportion of neuropathy-free subjects, and longitudinal follow-up may disclose a high transition rate to confirmed neuropathy.

Abstract 118LB

HCV Resistance to Peg-Interferon/Ribavirin Therapy Is Associated with Increased Immune Activation in HIV/HCV Co-infected Patients

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Background

HIV-infected patients co-infected with HCV have modest responses to anti-HCV therapy relative HIV-uninfected individuals. The purpose of the study is to examine gene expression patterns in PBMC of HIV/HCV co-infected patients to identify biological processes that distinguish responders from non-responders following 48 weeks of peg-interferon- α -2b and ribavirin therapy.

Methods

PBMC gene expression profiles from 15 patients pre- and post-anti-HCV therapy were determined using the Affymetrix U133A GeneChip (~22,000 genes). Patients were grouped as either non-responders (n = 5), relapsers (n = 7), or responders (n = 3) based on HCV viral load following therapy. Gene expression values were determined using MAS5 and significant differences in gene expression determined by ANOVA. Differentially expressed genes were grouped using K-means clustering and functional category enrichment was performed using EASE analysis.

Results

By treatment in all patient groups, 75 genes were induced and were significantly associated (p <0.0001) with interferon induction, immune response, and anti-viral response gene classification terms. Pre-therapy levels of these genes were highest in non-responders suggesting an elevated state of immune activation in these patients. A cluster of 278 genes exclusively up-regulated in non-responders prior to therapy also contained genes associated with immune activation. Elevated immune activation in non-responders prior to therapy was confirmed by flow cytometric analysis and clinical monitor assays which showed elevated levels %CD4+CD25+ cells, %CD4+CD45RO+ cells, B cell numbers, serum ALT, and serum AST. No relationship to HCV genotype was found among the patient groups.

Conclusions

Increased levels of immune activation in HIV-infected patients have been associated with poor prognosis and resistance to HAART and IL-2 therapy. Gene expression and clinical monitoring profiling of samples from HIV/HCV-co-infected patients also suggests a link between elevated immune activation and resistance to anti-HCV therapy and may provide a means to predict, in advance of treatment, which patients will fail anti-HCV therapy. The increase immune activation

state induced by HIV-1 infection may explain the lower response rate to HCV therapy in HIV-infected patients.

HIV/HCV Co-Infection

Abstract 110

A Randomized, Controlled Trial of PEG-Interferon-alfa-2a plus Ribavirin vs Interferon-alfa-2a plus Ribavirin for Chronic Hepatitis C Virus Infection in HIV-co-infected Persons: Follow-up Results of ACTG A5071

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Background

Chronic hepatitis C virus (HCV) is a major morbidity in persons infected with HIV. Treatment of HCV in HIV co-infection has been associated with poor responses and frequent intolerability. We conducted the first randomized trial of the efficacy and safety of peginterferon plus ribavirin vs interferon plus ribavirin for treatment of chronic HCV in HIV co-infection.

Methods

A total of 133 subjects were randomized to 180 mg of peginterferon--2a (PEG) weekly for 48 weeks or to interferon--2a (IFN) 6 MIU 3 times weekly for 12 weeks followed by 3 MIU 3 times weekly to complete 48 weeks. Both arms received ribavirin in a dose-escalation schedule from 600 mg/d to 1000 mg/d. At week 24, subjects who failed to achieve HCV clearance underwent liver biopsy, and medications were continued for virologic response (HCV RNA < 60 IU/mL) or histologic response (HR: >2 point drop in hepatic activity index).

Results

As previously reported (CROI 2002, LB15), week 24 VR was 44% with PEG/ribivirin vs 15% with IFN/R ($p = 0.0003$). End of treatment virologic response was 41% with PEG/ribivirin vs 12% with IFN/ribivirin ($p = 0.0001$). Within the PEG/ribivirin arm, end of treatment virologic response was 29% for HCV genotype 1 versus 80% for genotype non-1 ($p = 0.0007$). PEG/ribavirin was associated with a significantly higher sustained virologic response (HCV <60 IU/mL 24 weeks after end of therapy) than IFN/ribivirin (27 vs 12%, $p < 0.03$). Within the PEG/ribivirin arm, sustained virologic response was only 14% for genotype 1, compared with 73% for genotype non-1 ($p = 0.0007$). Independent predictors of sustained virologic response included receipt of PEG/ribivirin, HCV genotype non-1, no prior injection drug use, and a detectable HIV-1 RNA at entry. Histologic response was observed in 36% of virologic nonresponders and in 52% of virologic response who underwent liver biopsy. Both regimens were well tolerated. No loss of HIV disease control was observed. Failure to achieve >2-log

HCV RNA reduction at week 12 uniformly predicted failure to accomplish sustained virologic response (100% negative predictive value). Similar frequencies of flu-like symptoms, depression, and laboratory abnormalities were observed in each arm, and premature discontinuation rates were low in each arm (12%).

Conclusions

PEG/ribavirin is superior to IFN/ribavirin in the treatment of chronic HCV in HIV-co-infected persons and is well tolerated without adverse effect on HIV disease. The marked genotype discrepancy in sustained virologic response indicates that strategies to improve outcome in genotype 1 HCV are needed. These regimens may provide clinical benefit even in the absence of virologic clearance.

Abstract 111

Relationships between Hepatitis C Virus-specific Immune Responses and Outcomes of Treatment with Interferon and Ribavirin in HIV/HCV Co-infection

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Background

The relationship between HCV-specific immune responses and outcome of treatment with interferon (IFN) and ribavirin (RBV) is not well defined, but may allow us to better explain patient characteristics associated with treatment effectiveness. We hypothesized that individuals with more vigorous HCV-specific Th1-like immune responses would be more likely to clear HCV on treatment.

Methods

A5071 compared PEG-IFN-a-2a or standard IFN, both with RBV, in 133 subjects, with a primary endpoint of virological response at 24 weeks and a secondary endpoint of sustained virological response (HCV <600 IU/mL 24 weeks after therapy end). PBMC were isolated at baseline (n = 108 representative subjects), week 24 (n = 93) and week 72 (n = 57). ELISpot tests were performed for IFN-g and IL-10 using HCV antigens core, NS3 and NS5, Candida, and PHA. Mean spot-forming cells (SFC) in control wells were subtracted from antigen wells and reported as SFC/million PBMC. Data were analyzed using nonparametric methods and recursive partitioning (CART).

Results

The median baseline CD4 count was 486 (range 177 to 1001). Consistent with prior reports of low frequency HCV-specific responses, median values for HCV-specific responses were 0 at baseline, week 24, and week 72. Among those with responses, the range of HCV-specific responses was diminished at 24 weeks compared to baseline. Median values for IFN-g secretion to Candida at baseline, week 24 and week 72 were, respectively, 24 SFC, 13 SFC, and 16 SFC while for IL-10 they were 1.3 SFC, 0 SFC, and 4.7 SFC. Overall sustained virologic response in this trial was 19.4%. In univariate analysis, there were no differences between subjects with sustained virologic response and no sustained virologic response in terms of IFN-g or IL-10

secretion to HCV proteins or Candida at baseline, week 24, or week 72. There was also no correlation between entry CD4+ cell count and baseline or week 24 HCV-specific or Candida responses. In a multivariable CART model, predictors of sustained virologic response were (in hierarchical order) genotype non-1, a <2 SFC decrease in IFN-g secretion to NS5 between baseline and week 24, a < 103 SFC decrease in IFN-g secretion to Candida, HAI score for fibrosis >1, and age <46 years, with a sensitivity of 0.95 and specificity of 0.64.

Conclusions

HCV-specific and recall immune responses diminished during treatment with IFN/RBV in this cohort of persons co-infected with HIV and HCV. A relative preservation of Th1-like HCV-specific immune responses at week 24 was predictive of sustained virologic response, and immune responses augmented clinical parameters in predicting sustained virologic response.

Abstract 112

Final Results of APRICOT: a Randomized, Partially Blinded, International Trial Evaluating Peginterferon alfa-2a (40KD) (PEGASYS) + Ribavirin (COPEGUS) vs Interferon Alfa-2a + Ribavirin in the Treatment of HCV in HIV/HCV Co-infection

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Background

The AIDS Pegasys Ribavirin International Co-infection Trial (APRICOT) was designed to evaluate the safety and efficacy of HCV therapies approved for patients with HCV mono-infection in patients with HIV/HCV co-infection.

Methods

868 HIV/HCV co-infected subjects in 19 countries were randomized to 48 weeks of treatment with interferon alfa-2a 3 MIU tiw (IFN) plus 800mg/d ribavirin (RBV), peginterferon alfa-2a (40KD) 180 mcg qw (PEGASYS) plus placebo, or PEGASYS 180 mcg qw plus 800 mg/d RBV. Eligible subjects were HCV RNA and HCV antibody positive, had compensated liver disease, a CD4+ count >100 cells/mL, and stable HIV disease, with or without antiretroviral therapy (ART). The primary endpoint, sustained virological response (SVR), was defined as HCV RNA <50 IU/mL at the end of 24 weeks of treatment-free follow-up (week 72), determined by the COBAS AMPLICOR HCV Test v 2.0. SVR rates were compared by Cochran-Mantel-Haenszel test stratified by geographical region, genotype and CD4+ count using a closed testing procedure.

Results: 860 subjects received study drugs. Final week 72 results are presented in the table.

	IFN/RBV (A) (N=285)	PEGASYS/placebo (B) (N=286)	PEGASYS/RBV (C) (N=289)
Baseline Characteristics			
Male (%)	81	82	80
Caucasian (%)	78	79	80
Age (y) ^a	407.6	407.4	407.9
HCV RNA (10 ³ IU/mL) ^a	52085954	63546429	56166434
ALT (IU/L) ^a	8753	8857	8550
HCV genotypes 1, 2, 3, 4, other (%)	60, 5, 26, 8, <1	61, 6, 26, 7, 0	61, 4, 28, 6, 0
HIV RNA (copies/mL) ^b	50	50	50
CD4+ (cells/mL) ^a	542270	530265	520277
Receiving ART (%)	84	85	84
Cirrhosis/bridging fibrosis (%)	16	16	15
Safety Outcome (%)			
Treatment discontinuations			
Overall	111 (39)	90 (31)	72 (25)
AEs or lab abnormalities	44 (15)	47 (16)	43 (15)
Serious AEs (trt-related ^c)	15 (5)	28 (10)	24 (8)
Deaths (overall/trt-related ^c)	3/1	5/0	4/1
Neutropenia (<0.5 x 10 ⁹ /L)	1 (<1)	37 (13)	31 (11)
HCV Virological Outcome (%)			
End-of-treatment	41 (14)	95 (33)	143 (49)
SVR			
Overall	33 (12)	58 (20) p=.0078 vs A	116 (40) p<.0001 vs A p<.0001 vs B
HCV genotype 1	12/171 (7)	24/175 (14)	51/176 (29)
HCV genotypes 2&3	18/89 (20)	32/90 (36)	59/95 (62)
^a MeanSD			
^b Median			
^c Considered possibly/probably related			

Conclusions

Based on an SVR of 40%, PEGASYS + COPEGUS is the preferred treatment for HCV in co-infected patients. Further analysis of efficacy and safety data is ongoing to delineate the benefit/risk of the study treatment in specific subpopulations.

Abstract 113

Intrahepatic T-cell Responses to Hepatitis C Virus in Patients Co-infected with HCV and HIV prior to anti-HCV Therapy

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Background

In patients chronically infected with hepatitis C virus (HCV), whether co-infected or not with HIV, T-cell responses are often undetectable in peripheral blood. We analyzed the strength and specificity of HCV-specific CD8 and CD4 T-cell responses in the liver of HCV/HIV co-infected and HCV mono-infected patients.

Methods

Liver biopsies from 10 HCV/HIV patients (median CD4 count: 456/mm³; ranges: 283 - 630) and 8 HCV patients were studied. CD8 and CD4 T cells were expanded from the intrahepatic lymphocytes. CD8 T cells were co-cultured with autologous EBV-transformed B-cell lines infected with recombinant vaccinia viruses expressing the HCV core/E1, E2(NS1)/NS2, E2/NS2/NS3, NS4, NS5a, and NS5b or a control gene (lac). A pool of cytomegalovirus, Epstein Barr and influenza virus peptides (CEF) was used as a control. CD4 T cells were co-cultured with recombinant HCV proteins (core, NS3, and NS5) and irradiated autologous PBMC. Virus-specific interferon- γ production was determined by ELISA. Results were expressed in number of spot-forming-cells (SFC)/1x10⁶ cells and analyzed individually for each studied HCV protein as well as a sum of responses using nonparametric statistics.

Results

A vigorous and polyclonal intrahepatic CD8 response to HCV were detected in 7/10 HCV/HIV patients with median total frequencies of 638 SFC/1x10⁶ cells (range: 14 - 5700) and were not significantly different from those in HCV patients, detected in 7/8 patients (median; range: 647; 10 - 1941). Responses to CEF were significantly higher in coinfecting (1927; 47 - 4000) than in mono-infected (393; 0 - 1433) ($p = 0.04$). Intrahepatic lymphocytes versus PBMC anti-HCV CD8 responses were compared for 3 patients and found to be higher in the liver than in peripheral blood. Intrahepatic CD4 responses also did not differ between HCV/HIV and HCV patients (32 and 81 SFC/1x10⁶ cells, respectively; 0 - 235). Interestingly, there was a positive correlation between intrahepatic CD8 and CD4 responses to HCV ($r = 0.59$, $p = 0.03$). Intrahepatic CD8 responses were not correlated with CD4 counts or liver disease in this small cohort.

Conclusion

These results show a presence of vigorous and polyclonal HCV-specific CD8 T-cell responses in the liver of patients with chronic hepatitis C even in the presence of HIV, which correlated with intrahepatic HCV-specific CD4 responses, but not with peripheral CD4 counts. Future studies will determine the role of these cells in liver fibrosis.

Abstract 114

Frequency of Functional HCV-specific CD8+ Cells Depends on Total CD4+ Counts in HIV-1/HCV Co-infection: Implications for Immune Reconstitution

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Background

Virus-specific CD8+ cells play an important role in control of both SIV in macaques and HCV in chimpanzees, but no animal model has adequately studied HIV/HCV co-infection. We performed cross-sectional analysis in a large cohort of co-infected humans to determine the effects of HIV on HCV-specific functional immunity.

Methods

We studied 61 HIV+/HCV+ co-infected and 22 HIV-/HCV+ mono-infected individuals. No subject had ever received interferon therapy for chronic HCV. To determine comprehensively the HCV-specific CD8+ response in peripheral blood, we applied established approaches using a matrix IFN-g ELISpot with 494 peptides that span the entire genome, verifying novel responses by generation of specific T-cell lines and testing by intracellular cytokine staining. HIV-1 responses were determined using analogous comprehensive approaches. Tetramers were then used for further analysis.

Results

We detected ex vivo HCV-specific CD8 cells in 29/61 (47.5%) of co-infected and in 9/22 (40.9%) of mono-infected individuals. Single tetramer responses were as high as 3.6% of circulating CD8 cells. When analyzing persons with chronic HCV viremia (46 HIV+ versus 22 HIV- subjects), there were no differences in breadth ($p = 0.58$) or magnitude ($p = 0.53$) between the mono- and co-infected groups. However, a significant relationship emerged between peripheral CD4 cell counts and breadth ($r = 0.44$, $p < 0.001$) and magnitude of HCV-specific responses ($R = 0.40$, $p = 0.002$). This relationship was significant whether when analysis was restricted to HAART status and to those with genotype 1. In contrast, no such correlation existed for HIV-1 responses. Longitudinal data on subjects followed on HAART and phenotypic data will also be presented.

Conclusions

Surprisingly high frequencies of HCV-specific CD8 T cells are detected in HIV infection and did not differ from those without HIV. Only when CD4 cells are depleted due to progressive HIV is the HCV-specific CD8+ response significantly diminished. Conversely, these results suggest that functional immunity specific for HCV may augment on HAART, in contrast to HIV-1 responses which decline. These results shed insight into the relationship between CD4+ and CD8+ cells in a human viral infection. Moreover, these data provide rationale for further detailed longitudinal studies on HAART, to study prospectively immune reconstitution in co-infected subjects.

Abstract 117LB

Final Results of ANRS HC02-RIBAVIC: A Randomized Controlled Trial of Pegylated-Interferon-alfa-2b plus Ribavirin vs Interferon-alfa-2b plus Ribavirin for the Initial Treatment of Chronic Hepatitis C in HIV Co-infected Patients

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Background

The need to treat hepatitis C has become a significant issue in HIV-infected subjects. We compared the safety, tolerability, and efficacy of a 48-week course of the standard (IFN--2b: 3

MIU x 3/week, n = 207) (INF group) to the pegylated (PEG-IFN--2b: 1.5 -m/kg x 1/w, n = 205) interferon (PEG group) both combined with ribavirin (800 mg/d, approximately 12 mg/kg/d).

Methods

A randomized, multicenter, parallel-group, open-label trial. Inclusion criteria were: HCV-RNA-positive and abnormal liver histology, CD4 >200, stable HIV RNA, stable HAART or off HAART. Primary endpoint was sustained virologic response (SVR): loss of detectable serum HCV RNA at week 72 of follow-up.

Results

The 412 patients (40 years old, 74% male, 79% injection drug users [IDU]) were given HAART in 82%. Mean CD4 cell count was 514 + 229/mL, HIV RNA < 400 in 66% (mean HIV load in others: 3.7 + 0.7 logs). CDC class was A, B, and C in 53, 31, and 17%, respectively. HCV genotypes were 1 or 4 in 58%, 3 in 34%, and others in 8% (mean HCV load: 5.9 + 0.7 logs). The mean pre-treatment Metavir score was A 1.8 + 0.7, F 2.3 + 1.0, 39% of patients had F3-F4 of which 17% had sustained normal ALT. Baseline variables at entry were not different between groups.

Treatment discontinuation occurred in 167 patients (42%) (86 IFN, 81 PEG) and severe adverse events in 127 (31%) (64 IFN, 63 PEG), including 6 symptomatic hyperlactatemia and 5 acute pancreatitis. A decrease was observed at week 12 of treatment, in INF and PEG groups respectively, significant for Hb (-1.4 g/dL vs -1.8, p = 0.002) and platelets (-19,000 vs -33,000, p = 0.04), not significant for neutrophils (-692 vs -1071), lymphocytes (-543 vs -662), or CD4 cells (-116 vs -124).

SVR was achieved in 37 (18%) of IFN patients vs 54 (26%) of PEG patients, p = 0.031. In those who did not discontinue treatment, response rates were (week 4: 12 % vs 20%; week 12: 34% vs 41%; week 24: 41% vs 54%; week 48: 34% vs 52%; week 72: 26% vs 35%). Virologic response at week 12 predicted SVR with 87% Positive Predictive Value and 87% Negative Predictive Value. SVR varied with genotypes 1 or 4 (11%) vs 3 or others (43%), but not with the Metavir score or the ribavirin dose adjusted for body weight. In responders, a significant decrease in Metavir scores F (-0.4 + 0.7) and A (-1.0 + 0.7) was observed.

Conclusions

In HIV/HCV co-infected patients, the combination of IFN--2b and ribavirin including the pegylated form of INF is associated with a superior HCV virologic response and a quite similar adverse-event profile.

HIV/HCV Transplantation

Poster 826

Patient and Graft Outcomes following Solid Organ Transplantation

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Background

HIV-infected patients undergoing transplantation may experience HIV disease progression induced by immunosuppressants and/or accelerated graft failure due to HIV or its treatment. Alternatively, they may experience patient and graft survival rates similar to other patients.

Methods

A pilot, single center, non-randomized, longitudinal evaluation of patient and graft survival and post-transplant complications in subjects who received a liver or kidney transplant and were treated with antiretrovirals and immunosuppressants.

Results

Of the total, 14 subjects received kidney transplants, 9 received liver transplants, and 1 received a liver/kidney transplant (n = 24) between 3/00 and 9/03. Subjects included 23 men and 1 woman, with a median age of 45 (15 to 64); 54% were white, 33% African American, 8% Asian, and 4% Latino. Four (17%) subjects had a prior history of 5 opportunistic complications (CMV, cryptococcal meningitis, MAC, KS, and TB).

Median pre-transplant CD4+ T-cell count was 407 (104 to 973). HIV RNA was undetectable in kidney recipients; median HIV RNA was <75 (<75 to 55,100) in liver recipients. HCV infection was present in 4 (40%) liver and 4 (29%) kidney recipients.

Median follow-up as of October 1, 2003, is 480 days (8 to 1254). Two subjects died: 1 liver recipient with recurrent HCV infection (15 months) and 1 kidney recipient with pneumonia (6 months). There was one case each of the following: Candida esophagitis, CMV esophagitis, and pulmonary Aspergillus infection. There was no recurrence of prior opportunistic infections.

At follow-up, the median CD4+ T-cell count was 255 (8 to 902) and HIV RNA was <75 (<75 to 9600). Rejection occurred in 10 (71%) kidney recipients, the liver/kidney recipient, and one liver recipient. There were 5 cases of delayed graft function in kidney recipients and 1 kidney graft loss due to rejection. Median creatinine is 1.6 (1.1 to 3.2) in kidney recipients. One liver recipient required re-transplantation due to a small for size graft lesion. Recurrent HCV has been documented in 2 liver recipients, 1 of whom received HCV treatment, and progressive HCV in no kidney recipients.

Conclusions

Liver and kidney transplantation appears to be associated with good patient and graft survival and minimal evidence of HIV disease progression despite CD4+ T-cell declines with rejection treatment. There is an unexpectedly high rate of kidney rejection. A multi-site study will definitively address the safety and efficacy of this intervention.

Poster 827

Orthotopic Liver Transplantation in 15 HIV-1-infected Recipients: Evaluation of Spanish Experience in the HAART Era (2002-2003)

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Background

The safety and efficacy of orthotopic liver transplantation (OLT) in HIV-1-infected patients is currently being re-evaluated in the HAART-era.

Methods

Prospective cohort study of all Spanish HIV-1-infected patients who underwent OLT. Inclusion criteria: Liver criteria were the same as for the non-HIV-1-infected population; no previous CDC stage C events except tuberculosis, pre-OLT CD4 cell count greater than 100 cells/mm³ and undetectable plasma RNA HIV-1 viral load on HAART or detectable plasma viral load off HAART with post-transplant suppression predicted; and no heroin or cocaine abuse for the last 2 years and no alcohol abuse for the last 6 months. OLT and HIV characteristics at base line and during follow-up were collected using a standardized CRF.

Results

The first OLT in an HIV-1-infected patient was performed in January 2002. Six sites have transplanted 15 HIV-infected patients, 10 in the year 2003. Median (range) age was 38 (35 to 51) years, 80% of recipients were male and former drug use (73%) was the most common HIV-1 risk factor. HCV-related cirrhosis (93%) was the leading indication for OLT. Pre-OLT Child-Pugh class was C, B or A in 6, 7 and 2 cases, respectively. The latter two cases had hepatocellular carcinoma. Pre-OLT antiretroviral therapy was given in 13 cases (efavirenz-based HAART in 9, three NRTI in 3 and protease-inhibitor-based HAART in 1 patient). Median (range) CD4 cell count pre-OLT was 247 (142 to 589) cells/mm³ and 12 patients (80%) had undetectable plasma viral load. 13 recipients received a cadaveric graft and two a graft from a living donor. Immunosuppression therapy was the standard in each center. There was no operative mortality.

Median (range) follow-up was 6 (1 to 21) months. None of the patients required re-transplantation. All patients received HAART after OLT. Only one patient died (7%) at 3 months. Death was non-HIV related. One patient had to stop HAART at 4 months because of massive liver steatosis. There was neither clinical nor immunological HIV-1 progression in the remaining cases except in one. Four subjects (27%) experienced rejection and 10 out of 13 (77%) patients with more than one month of follow-up have become HCV re-infected. Therapy with peg-interferon plus ribavirin was started in 3 cases.

Conclusions

OLT is a safe and effective procedure at short/mid-term for selected HIV-1-infected patients in the HAART era. However, HCV re-infection is a cause for concern.

Poster 828

Liver Transplantation in HIV-HCV Co-infected Patients

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Background

End stage liver disease in HIV-HCV co-infected patients is an emerging problem requiring to assess the benefit risk ratio of liver transplantation (LT). We started a prospective evaluation of LT in co-infected patients in December 1999 assessing several parameters: impact on the

immune system and HIV replication, drug interactions, mitochondrial toxicity and incidence of HCV relapse.

Methods

Up to December 2002, eleven HIV-HCV co-infected patients without history of opportunistic infection, were transplanted. At time of LT all patients were exposed to HAART, HIV plasma viral load was < 400 copies/mL and the median CD4 lymphocyte count was 350 cells/mm³ (range: 103-659). Immunosuppression therapy consisted of steroids and Tacrolimus. Anti HCV viral therapy was used when necessary and its benefit risk ratio was prospectively evaluated. Lastly, mitochondrial toxicity on the graft was studied by spectrophotometric analyses of the respiratory chain complexes and molecular analysis of mitochondrial DNA (mtDNA).

Results

At time of evaluation, the median follow-up is 18 months (range 3 to 45): 3 patients died, 4, 11, and 19 months after LT. Seven patients are in good condition and one patient is in poor condition. None of the patients developed opportunistic infection. Drug interaction was under control, only one patient developed a transient renal insufficiency. HCV replication started promptly after LT in all patients. Seven patients began pegylated interferon (PEG-IFN) and ribavirin therapy. This treatment was stopped in three patients because of intolerance. One patient showed a virological response and another a biochemical response and a decrease of liver fibrosis. At last biopsy, METAVIR score was staged F4 in 2 patients, F3 in 1, F2 in 2. Microvesicular steatosis was observed in nearly all patients. The ratio mtDNA nuclear DNA was low in 4 patients. A significant defect on the activities of respiratory chain was noted in five patients.

Conclusions

Liver transplantation in HV/HCV co-infected patients is feasible in a very selected population. Our experience do not suggest a deterioration of immune deficiency. Drug interaction is not a limiting problem. The early and severe relapse of hepatitis C suggest to start promptly an association of PEG-IFN and ribavirin. LT requires a multidisciplinary partnership.

Poster 829

Clinical Presentation and Outcome of Hepatocellular Carcinoma in HIV-infected Patients

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Background

Hepatocellular carcinoma (HCC) is an increasing cause of mortality in HIV+. The aim of the study is to identify clinical characteristics of HCC in HIV+ persons and to compare them with those observed in anti-HIV- subjects.

Methods

In this non-concurrent prospective case control study, we enrolled HIV+ subjects with a diagnosis of HCC defined according to EASL guidelines notified to 2 registries for tumors. All

cases of HCC diagnosed in HIV- subjects in the town of Brescia from 1995 to 1998 and all HIV- cases from the registry of the Cancer of the Liver Italian Project (CLIP) were enrolled as control groups. Data on each eligible case were collected through a standardized case record form. All patients were followed up for at least 2 years. Clinical characteristics at presentation and survival were compared between HIV+ and HIV- subjects by logistic regression and Cox's proportional hazard regression analysis.

Results

Of the 41 cases of HIV+ subjects with HCC, 1 received the first diagnosis in 1989, 2 in 1997, 2 in 1998, 2 in 1999, 6 in the year 2000, and 10 in the first 6 months of the year 2001; 33 cases have been observed in Italy and 8 in Spain. Their individual data have been compared with those of the 384 HIV- from the Brescia HCC study group registry and those of the 701 HIV- from the CLIP registry. Multivariate analysis adjusted for age and gender identified an association between HIV infection and higher prevalence of HCV infection (OR 11 vs Brescia HCC study group; $p = 0.005$ and $9 p = 0.006$ vs CLIP registry), and higher frequency of infiltrating tumors or extranodal metastasis at presentation (OR 11,8; $p < 0.001$ vs Brescia HCC study group and $17,3 p = 0.001$ vs CLIP registry). These variables were independently associated with HIV infection in both comparisons. HIV infection was associated with reduced survival independently from treatment, Child-Pugh status, portal invasion, serum alpha-fetoprotein, tumor morphology, and size (HR 1,63 $p = 0.015$ vs Brescia HCC study group and HR 1,5 $p = 0.013$ vs CLIP registry).

Conclusions

Our data suggest that HCC in HIV+ has a more aggressive clinical course that reduces the chances for cure. Thus preventive strategies for HCC should be implemented in the management of HIV-infected subjects.

HAV and HBV: Prevention and Treatment Issues in HIV Infected Persons

Poster 830

Response to Hepatitis A Vaccination in HIV+ Patients

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Background

Hepatitis A (HAV) is common in HIV+ patients. Superinfection with HAV in patients with chronic hepatitis C (HCV) can lead to fulminate hepatic failure. The USPHS/IDSA guidelines for Prevention Of Opportunistic Infections In Persons with HIV recommends that all susceptible HIV patients at increased risk for HAV or with chronic liver disease, be vaccinated against HAV. Immune response to HAV vaccine has not been well studied in HIV positive patients. Our goal is to assess the immune response to HAV vaccination in HIV+ patients, and the effect of HIV viral load, CD4 count nadir, and CD4 count at vaccination and antiretroviral use (ART) on immune response rates to HAV vaccination in HIV+ patients.

Methods

Retrospective analysis of all HIV positive patients seen at HSR and CVAMC between 1/1/2001 and 9/30/2003 who were tested for HAV antibodies. Patients with negative HAV antibody received 2 HAV vaccines (HAVRIX) 6 to 12 months apart. Post HAV antibody response was measured after the second vaccine. Univariate and multivariate analysis was done to determine predictors of response to vaccine.

Results

Of 485 patients evaluated, 207 had a positive prevaccine HAV antibody result. Of the 278 included, 103 patients have completed their HAV vaccination series and have post vaccine HAV antibody results. Of 103 (49%) patients, 51 had positive post vaccine HAV antibody results (responders). There was no difference in age, race, HIV risk group, ART use, or HCV exposure between vaccine responders and nonresponders; 50% of responders had CD4 nadir <200 compared with 62% of nonresponders ($p = 0.25$). The mean nadir CD4 count was lower in nonresponders compared with responders, but this did not reach statistical significance. In univariate analysis vaccine responders were more likely to be female (40% vs 13.5%, $p = 0.001$), have a higher CD4 count at vaccine (491 cells/mm³ vs 361 cells/mm³, $p = 0.03$) and lower viral load at vaccine (5,770 copies/mL vs 29,058 copies/mL, $p = 0.02$). Responders were less likely to have a CD4 count <200 cells/mm³ at vaccine compared with nonresponders (14% vs 35%, $p = 0.02$). Multivariate analysis showed that female sex and higher CD4 count at vaccine were independent predictors of response to vaccine.

Conclusions

Of our HIV+ patients, 49% responded to HAV vaccine. This is much lower than reported rates of 100% in HIV- patients. Female sex and CD4 count at vaccine but not CD4 nadir predicted response to vaccine.

Poster 831

High Incidence of Fluctuations of Hepatitis B Serum Markers in HIV-infected Patients

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Background

Co-infection of HIV+ patients with hepatitis B virus (HBV) constitutes a risk to hepatotoxic reactions and possibly long-term liver damage. Flares of hepatitis due to HBV reactivation has been described in a number of case reports. Longitudinal studies on HBV serum markers has not been systematically investigated yet.

Methods

All patients that ever attended the HIV clinic of the Bernhard Nocht Institute and who were positive for HBV core antibodies (anti-HBc) at least once were eligible for a retrospective analysis over 20 years (1983 to 2003). HBs antigen (HBsAg) and HBs antibodies (anti-HBs) were measured from samples stored at -80°C at least in the first and last available serum sample, at times of HIV treatment change, and in-between, if a change of the serostatus was observed.

Results

Of 504 eligible patients, 384 had at least 2 serum samples and clinical data available more than three months apart. In the latter subgroup, HBs-Ag was negative in 61.2% and positive in 13%. A seroconversion from HBs-Ag negative to positive occurred in 12% and vice versa in 4.4%. Fluctuating detection of HBs-Ag in both directions was detected in 9.4%. These figures were observed for anti-HBs in 42.2%, 41.9%, 2.1%, 8.9%, and 4.2%, respectively. There was a statistically significant correlation with hepatitis C virus antibody status (anti-HCV), such that in anti-HCV positive patients anti-HBs ($p < 0.001$) as well HBs-Ag ($p = 0.011$) was less frequent as compared to anti-HCV negative patients. The serum of four patients without signs of acute hepatitis was initially negative for anti-HBc. Three of them were HBs-Ag positive, one anti-HBs positive, and all HBV DNA positive. Three patients experienced a severe hepatitis, followed by development on HBs antibodies.

Conclusions

Changes of the hepatitis B serostatus in HIV-infected patients is an unanticipated frequent phenomenon. This raises interesting questions on the hepatitis B immunology in HIV infection. With respect to the hepatotoxic potential, repeated measurements of hepatitis B markers should be considered.

Poster 832

Quantification of Hepatitis B Virus-specific T-cell Responses in HIV/HBV Co-infected Individuals

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Background

In HIV/HBV co-infected patients with persistent HBV replication receiving antiretroviral therapy (ART), immune restoration has been associated with an increased progression of liver disease, worsening hepatitis and severe liver failure in some individuals, while in others, ART is associated with the generation of HBV-specific immunity and HBeAg seroconversion. In order to better understand HBV immunopathogenesis in the setting of HIV infection, better methods are needed to study HBV-specific T cell immunity.

Methods

A peptide library to the entire genome of HBV (genotype A) was designed as 15-mers, overlapping by 11 amino acids allowing analysis of both CD4⁺ and CD8⁺ T-cell responses. An additional 150 15-mers were designed to areas of inter-genotype heterogeneity for genotypes B, C and D resulting in a total of 500 peptides. A panel of 21 9-mer and 10-mer peptides, previously defined as HLA-A2 restricted CTL epitopes were also generated. In HIV-infected patients, peptide pools to HIV env, gag, pol and accessory genes (obtained from the NIH reagent database) were analysed on the same blood sample. Using these peptides, in pools of up to 100, HBV-specific responses were assessed by ELISpot and/or intracellular cytokine staining (ICS) using antibodies to CD3, CD4, CD8, and interferon-g (IFN-g).

Results

Background responses were initially evaluated using HBV-negative donors (n = 13). Blood was obtained from chronic carriers of HBV (n = 37) including patients treated with lamivudine (n = 23), and/or co-infected with HIV and treated with tenofovir or lamivudine (n = 14). Detection of spot forming cells (SFC) by ELISpot was far more frequent using peptide pools compared to previously defined HLA-A2 epitopes. Using ICS, HBV-specific CD8+IFN-g+T cells were detected more frequently (including percentage and number of positive peptide pools) in individuals taking anti-HBV therapy. Overall, HBV-specific CD4+IFN-g+ T cells were far less frequent than CD8+ IFN-g+ T cells. There was a significant reduction in CD4+ IFN-g+ T cells in the setting of co-infection with HIV but no significant difference in the magnitude or breadth of CD8+ IFN-g+ T cells. HBV-specific responses were significantly lower than HIV-specific responses in all co-infected individuals.

Conclusions

Co-infection of HBV and HIV is primarily associated with a reduction of HBV-specific CD4+ T-cell responses with little effect on HBV-specific CD8+ T-cell responses.

Poster 834

Efficacy of Tenofovir Disoproxil Fumarate in Hepatitis B Virus in HIV-co-infected Patients: The TECOVIR Study

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Background

Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue with dual activity against both HIV and HBV. Small sample sized, pilot open studies have suggested TDF efficacy against wild-type, precore and lamivudine resistant HBV. The objective was to evaluate efficacy of TDF (300 mg once a day), administered as a part of antiretroviral therapy, in a large cohort of HIV/HBV co-infected patients.

Methods

HIV/HBV co-infected patients who received TDF for at least 2 weeks and who had stored serum samples at the beginning and during TDF therapy were included. Clinical, biological and virological data were retrospectively recorded. Serum HBV DNA was measured on stored samples by the Amplicor Monitor Roche 2.0 (sensitivity 2.3 log₁₀ copies/mL). Baseline was the day of TDF initiation and the end point was the day of the last available stored serum sample during TDF therapy.

Results

A total of 119 patients (mean age 42.4 ± 7.1 years) were included. The median follow-up period was 8.0 (1 to 24) months. All the patients but 5 (97%) were receiving lamivudine (150 mg twice daily) at baseline. Median CD4 count and HIV RNA at baseline were 337 (3 to 1174) cells/μL and 2.8 (1.3 to 6.1) log₁₀ copies/mL, respectively. Fifty-two patients (48%) had an HIV RNA <400 copies/mL. HBeAg and anti-HBe Ab were positive at baseline in 73 patients (68%) and 29 patients (27%), respectively. HBV DNA was detectable at baseline in 88 patients (84%). Of

these patients, 83 (95%) were receiving lamivudine at TDF initiation. After a median period of 9 (1 to 24) months HBV DNA became undetectable in 28 (32%) patients. In this group of patients, the median reduction from baseline of serum HBV DNA (8.0; 2.4 to 8.8 log₁₀ copies/mL) was -3.8 (-6.4; -2.5) log₁₀ copies/mL (p <0.0001). Serum HBeAg became negative in 5 patients after > 6 months of treatment, 3 of them seroconverted to anti-HBe Ab. Serum HBV DNA remained undetectable in the 16 of 17 patients with negative PCR at baseline during TDF therapy (5.0; 1 to 17 months).

Conclusions

The results of this large cohort demonstrate the anti-HBV efficacy of TDF (300 mg once daily), given for a median period of 9 months as a part of antiretroviral therapy, in HIV infected patients with HBV replication and mostly receiving lamivudine.

Poster 835

3-Year Treatment with Adefovir Dipivoxil in Chronic Hepatitis B Patients with Lamivudine-resistant HBV/HIV Co-infection, Results in Significant and Sustained Clinical Improvement

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Background

Adefovir dipivoxil (ADV), 10 mg, has shown efficacy and safety in a broad range of populations with chronic hepatitis B over 48 to 96 weeks, including treatment-naïve and Lamivudine-resistant (LAM-R) HBV patients. This study reports the first 3-year long-term safety and efficacy data with ADV in patients with LAM-R HBV, co-infected with HIV.

Methods

Patients failing LAM received 3 years of ADV added to pre-existing anti-retroviral therapy including LAM. Patients were seen every 4 weeks for 48 weeks and then every 12 weeks. At each visit, serum ALT, serum HBV DNA (Roche Amplicor PCR), HBV serological markers, plasma HIV RNA (Roche HIV Monitor LLQ 2.3 log₁₀ copies/mL) and CD4 count were evaluated.

Results

Of the 35 patients enrolled, 28 completed 144 weeks of ADV. Median serum HBV DNA declined from baseline 8.75 (Q1-Q3, 8.41 to 8.93) log₁₀ copies/mL by 3.98 (3.48 to 4.79), 4.81 (3.86 to 5.31), and 5.45 (3.94 to 6.15) log₁₀ copies/mL at weeks 48, 96, and 144, respectively (p <0.0001). Thirteen patients (46%) achieved undetectable serum HBV DNA levels (≤ 3 log₁₀ copies/mL) at week 144. In 3 patients cessation of lamivudine had no effect on HBV DNA levels. One patient had a rebound in serum HBV DNA (confirmed ³1 log₁₀ copies/mL increase from nadir) while on ADV therapy. No HBV or HIV resistance mutations associated with ADV were identified up to week 96. Week 144 resistance surveillance is ongoing. Median ALT was reduced by 16, 44.5, and 46 IU/L and ALT normalized in 19%, 37%, and 64% after 48, 96 and 144 weeks, respectively. No serious adverse events related to ADV occurred throughout the study period and there were no significant changes in HIV RNA throughout the study. No serum creatinine elevations related to ADV were seen. CD4 cell counts and serum HIV RNA levels remained stable throughout the study

Conclusions

Long-term treatment with ADV (10 mg once daily) was well tolerated and resulted in significant and sustained reduction in serum HBV DNA and ALT over 3 years of therapy, with the magnitude increasing with treatment duration and there was no loss of suppression. No HBV- or HIV-resistance mutations associated to ADV were identified.

Poster 836

Emtricitabine Therapy for Hepatitis Infection in HIV+ Patients Co-infected with Hepatitis B Virus: Efficacy and Genotypic Findings in Antiretroviral Treatment-naïve Patients

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Background

Chronic hepatitis B virus (HBV) infection affects 8% to 11% of patients with HIV infection. Antiretroviral medications with activity against both viruses, such as emtricitabine (FTC), may provide benefit by controlling both HIV and HBV replication.

Methods

Patients were enrolled in one of three, 48-week studies evaluating emtricitabine as part of a triple drug regimen for the treatment of HIV infection. Regimens included FTC + didanosine + efavirenz (n = 286), FTC + stavudine + efavirenz or nevirapine (n = 234), and FTC + stavudine with either emvirine (an investigational non-nucleoside reverse transcriptase inhibitor) or abacavir (n = 564). Samples from patients shown to be HBsAg+ at baseline and exposed to >6 months of FTC with demonstrable HIV RNA suppression were evaluated for HBV DNA viral load and for genotypic findings. HBV DNA viral load analysis was performed on patient plasma using the Digene HBV Test Hybrid Capture II Assay with a lower limit of detection (LOD) of 4700 copies/mL. Genotypic analysis of the HBV polymerase was performed for baseline and week 48 samples that quantified >4700 copies/mL.

Results

We identified 39 HBsAg+ patients for analysis, with 24/39 (62%) having HBV DNA > 4700 copies/mL at baseline. For the 24 patients with detectable viremia, HBV viral load was determined every 12 weeks to week 48. At baseline, the median HBV DNA was 8.68 log₁₀ copies/mL. Seventeen patients were available for evaluation at week 48; 14 of whom (82%) had a greater than 5 log₁₀ decrease in HBV DNA, or had HBV DNA below LOD at week 48. Genotypic analysis of the HBV polymerase from the seven patients with detectable HBV DNA at week 48 showed that two had developed a mutation in the YMDD region (M204M/I) while none of the patients had developed the dual L180M/M204V mutations. Overall, the proportion of co-infected patients below LOD and the incidence of new mutations in this population was not different when compared to a subgroup of chronic HBV infected patients treated with emtricitabine for 1 year (95% CIs for the difference between groups were -22%, 36% and -16%, 21%, respectively).

Conclusions

Emtricitabine, as a component of HAART, produced potent suppression of HBV DNA in treatment naïve, HBV co-infected patients as shown by a decrease in HBV DNA levels, the

proportion of patients with HBV DNA levels below LOD and the low incidence of resistance associated mutations following 48 weeks of therapy.

Poster 837

Influence of HCV or HBV Infection on Efavirenz Plasma Concentrations in HIV-infected Patients

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Background

Therapeutic drug monitoring of efavirenz (EFV) may be of interest because low and high EFV plasma concentrations are associated with treatment failure and possibly with central nervous adverse effects, respectively. To date the influence of HCV and HBV co-infection on EFV plasma concentrations has not been evaluated.

Methods

This study was retrospectively conducted in 124 HIV-patients (78 with negative hepatitis serology, 25 HIV/HCV, and 21 HIV/HBV co-infected). All patients (32 female, 92 male) received 600 mg oral EFV once a day at bedtime in combination with other antiretroviral agents. EFV plasma concentrations were measured at steady state, at least 8h after the last drug intake using a validated HPLC method. Differences in efavirenz plasma concentrations were analyzed by a Kruskal-Wallis test and Pearson Chi-square with Fisher's test for small numbers.

Results

In non co-infected, HIV/HCV and HIV/HBV patients, mean \pm SD EFV plasma concentrations were 2923 \pm 1970 ng/mL, 3888 \pm 3372 ng/mL, 3114 \pm 2468 ng/mL respectively. EFV plasma concentrations were in the target values (i.e. 1000 to 4000 ng/mL) in 60/78 non co-infected patients and 33/44 HBV or HCV coinfection. EFV was overdosed (> 4000 ng/mL) in 14/78 non co-infected patients and 11/44 HBV or HCV coinfection ($p = 0.05$). In univariate analysis, coinfection with HCV ($p = 0.08$), ALAT ($p = 0.03$), and ASAT values ($p = 0.01$) at the time of EFV treatment, were associated with higher EFV plasma concentrations. Influence of sex and ethnic origin were not predictive of EFV plasma levels.

Conclusions: Co-infection with HCV or HBV were more frequently associated with an EFV plasma concentration (>4000 ng/ml) over the target value. Therapeutic drug monitoring of EFV may be of interest in these populations.

Neuropathogenesis: Viral Co-Factors

Poster 469

HIV, Hepatitis C, and Methamphetamine Dependence Independently Worsen Neuropsychological Performance

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Background

HIV, HCV, and Meth are each associated with central nervous system (CNS) complications. All 3 may injure the CNS by similar mechanisms, such as macrophage activation, oxidative stress, and direct neuronal injury. The objective of this study was to determine if HIV, HCV, and Meth are independently associated with NP performance.

Methods

We enrolled 401 subjects in a prospective study of the CNS effects of HIV and Meth. Subjects were recruited into 4 groups: HIV-Meth- (n=82), HIV+Meth- (n=110), HIV-Meth+ (n=115), and HIV+Meth+ (n=94). Meth+ subjects met DSM-IV criteria for dependence within 18 months but were not actively using meth, heroin, or cocaine. All subjects had standardized assessments, including NP tests, phlebotomy, and lumbar puncture. NP results were summarized as a global deficit score (GDS), a composite measure that adjusts for age, education, and ethnicity. HCV IgG and immune activation markers were measured by ELISA. HIV and HCV RNA levels were measured by RT-PCR. Data were analyzed using standard statistical methods, including non-parametric measures of association and linear regression. For some analyses, subjects were categorized by the number of risk conditions present (0, 1, 2, or all 3).

Results

HCV IgG was detected in 78 (19%) subjects, 67 (86%) of whom were Meth+. HCV+ subjects did not have advanced liver disease, based on albumin, transaminase, and platelet levels. They were 2.4 times more likely to be globally impaired, compared to those who were HCV- ($p<.001$). In the entire cohort, impairment worsened as the number of co-existing risk conditions increased: 0 (median GDS 0.21), 1 (.32), 2 (.47), or all 3 (.74) ($p<.001$). In a linear regression, HIV, HCV, and Meth were independently associated with worse GDS, even after adjusting for CD4 counts and antiretroviral use ($R^2=.10$, $p<.001$). HCV RNA levels in plasma were higher in those with memory, but not global, impairment (median 6.7 vs 5.9 log c/mL, $p=.05$). In CSF, HCV RNA was below 100 copies/mL in all specimens. Elevated immune activation markers in plasma and CSF were more frequently associated with HIV and HCV than with Meth.

Conclusions

HIV, HCV, and Meth independently cause neural injury, leading to global impairment. HIV and HCV may mediate neural injury, in part, by activating monocyte-derived macrophages, which can release neurotoxins and replicate HIV and possibly HCV. Meth may injure the brain by other mechanisms, such as oxidative stress.