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Pilot Study of Low Dose Daily Interleukin-2 (IL-2) Plus Pegylated-Interferon-alfa-2b (PEG-IFN) and Ribavirin (RBV) in Patients with HCV/HIV Co-Infection: ACTG A5088

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REVISED ABSTRACT

Background: HCV/HIV co-infected patients have diminished HCV virologic response to standard interferon-based therapies. We hypothesized that priming of immune responses to HCV might enhance response to standard HCV therapy. We conducted a pilot study to test the safety of a novel approach of initial immunostimulatory therapy with IL-2 followed by PEG-IFN/RBV plus IL-2.

Methods: Twenty-three HCV/HIV co-infected subjects with CD4 > 300 cells/uL and native to HCV therapy initiated IL-2 1.2 MIU/m2 s.c. qd for 12 weeks followed by the addition of PEG-IFN 1.5 ug/kg qwk and RBV 800-1400 mg/d (based on weight) for an additional 48 wks. The primary endpoint in this pilot trial was permanent treatment discontinuation prior to wk 24 due to toxicity/intolerance. End-of-treatment (wk 60) **and sustained virologic response** results are presented herein with virologic response (VR) defined as HCV RNA < 100 copies/ml (intent-to-treat).

Results: Subjects were 83% male; 65% White, 30% Black; and had a median age of 44 yrs. Median baseline values were: CD4 648 cells/uL and HCV RNA 7.5 million copies/mL. Twenty (87%) subjects had HIV RNA < 400 copies/ml at baseline. The majority of subjects (83%) were HCV genotype 1a or 1b. Two (9%) subjects discontinued treatment before wk 12 (while receiving only IL-2), 6 (26%) before wk 24, and 11 (48%) before wk 60. Discontinuations prior to wk 12 were due to suicide (n=1) and low grade toxicity/subject decision (n=1). Discontinuations after wk 12 were due to grade 4 anemia (n=1), non-response (n=1), nonadherence (n=1) and subject decision (n=6). Grade 3 or 4 adverse events were: fatigue (n=2), pain (n=1), diarrhea, (n=1), nausea/vomiting (n=1), neutropenia (n=5), anemia (n=1), and hyperglycemia (n=1). At the end of treatment at wk 60, 5 of 23 (22%; 95% confidence interval 7-44%) had VR. **Four of 23 (17%; 95% CI 5-39%) had sustained VR.** Median change in HCV RNA from baseline to wk 60 was -0.71 log10 copies/ml, and 6 (27%) had > a 2 log drop at wk 60. Of the 17 subjects with ALT elevations at study entry, 13 had measurements available at week 60: of these, 6 (46%) were normal. Median changes in CD4 count were +11, -102, -78, and -121 at wks 12, 24, 36, and 60.

Conclusions: Low dose IL-2 plus PEG-IFN and RBV was associated with a high discontinuation rate and did not enhance treatment efficacy in this pilot study. Although this study was not powered for efficacy, confidence intervals surrounding the treatment response rate suggest that this strategy should not be pursued in larger trials.

BACKGROUND

•Virologic responses to standard interferon-based therapies for HCV, including pegylated interferon/ribavirin, have been reported to be suboptimal in HIV-infected patients (Chung, 2002)

•Vigorous T-cell proliferative responses to HCV proteins are associated with viral clearance in HIV-uninfected patients with acute HCV (Lechmann, 1996), and cytotoxic lymphocyte activity correlates inversely with level of HCV viremia in chronic HCV monoinfection (Hiroishi, 1997)

•Administration of low dose, daily s.c. IL-2 to HIV-infected subjects has been reported to be well tolerated and result in increases in CD4 cell counts and delayed type hypersensitivity responses (Jacobson, 1996)

•We hypothesized that priming of immune responses to HCV with low dose daily IL-2 might enhance response to standard HCV therapy

•We conducted a pilot study to test the safety of a novel approach of initial immunostimulatory therapy with IL-2 followed by PEG-IFN/RBV plus IL-2.

Objectives

•Primary: To determine the safety of coadministration of low dose IL-2 with PEG-IFN alfa-2b + RBV in HCV/HIV coinfected patients

•Secondary: To explore the efficacy of this study therapy based on:
a) Presence/absence of HCV viremia at select time points
b) Achievement of biochemical response (normalization of ALT) and relative changes in HCV viremia at select time points

METHODS

Major Entry Criteria

•Age 18-65 years
•Documented HIV infection
•Stable (for > 8 weeks) or no antiretroviral therapy
•CD4 cell count > 300 cells/µL
•HIV RNA < 5,000 copies/ml
•Chronic HCV infection with detectable viremia
•Liver biopsy within 24 months demonstrating chronic hepatitis

Lab values within 30 d:
- Absolute neutrophil count ≥ 1000/µL
- Hemoglobin ≥ 10 g/dL for women, 11 g/dL for men
- Platelets ≥ 75,000 /µL
- ALT and AST ≤ 5 x upper limit of normal

•Absence of HBV coinfection
•Absence of decompensated cirrhosis

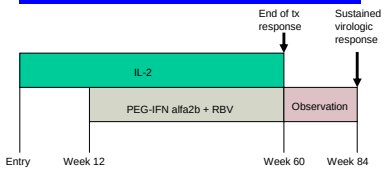
Statistical Methods

•Primary endpoint = voluntary or study-mandated permanent discontinuation of IL-2 and/or PEG-IFN prior to week 24 due to toxicity or intolerance

•Sample size: 23 evaluable subjects provides 80% power (1-sided alpha=.05) to detect a true drop-out rate of 25% and rule out the possibility that it is as high as 50%

•Subjects who discontinued therapy prior to week 24 due to HCV disease or study treatment are considered nonresponders whether endpoint information is available or not

STUDY DESIGN



Doses:

IL-2 1.2 MIU/m^2 s.c. QD

PEG-IFN alfa2b 1.5 µg/kg s.c. Q week

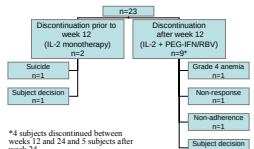
RBV 800-1400 mg/d based on body weight

RESULTS: SUBJECT CHARACTERISTICS

Baseline Characteristics

n	23
Male sex	19 (83%)
Race/Ethnicity White, non-Hispanic Black, non-Hispanic Asian/Pacific-Islander	 15 (65%) 7 (30%) 1 (4%)
Median age, years	44
Normal ALT	6 (26%)
Median HCV RNA, copies/ml	7,500,000
HCV Genotype 1A 1B 2B 4	 11 (48%) 8 (35%) 2 (9%) 2 (9%)
HIV RNA, copies/ml < 50 51-200 <400 200-1000	 13 (57%) 2 (9%) 5 (22%) 3 (13%)
CD4 cell count, cells/mm^3 Median 301-400 401-500 501-600 601-700 >700	 648 5 (22%) 4 (17%) 1 (4%) 6 (26%) 7 (30%)

SUBJECT DISPOSITION



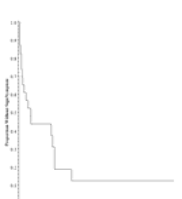
*4 subjects discontinued between weeks 12 and 24 and 5 subjects after week 24

RESULTS: SAFETY

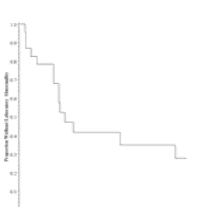
Grade 3 and 4 Adverse Events

Event	Number of Subjects
Grade 3	
Fatigue/Malaise	2
Ache/pain	1
Diarrhea/loose stools	1
Nausea/vomiting	1
Neutropenia	2
Grade 4	
Anemia	1
Hyperglycemia	1
Neutropenia	3

Time to First Moderate or Worse Sign/Symptom



Time to First Moderate or Worse Chemistry/Hematology Toxicity



RESULTS: EFFICACY

Achievement of Undetectable HCV RNA (< 100 copies/ml)

Week	N (%) Undetectable	N (%) Measured Detectable	N (%) Missing (considered detectable)	Total
12	0 (0%)	21 (91%)	2 (9%)	23
16	1 (5%)	18 (86%)	2 (10%)	21*
24	4 (17%)	15 (65%)	4 (17%)	23
36	4 (18%)	15 (68%)	3 (14%)	22*
60	5 (22%)	13 (57%)	5 (22%)	23
72	4 (18%)	10 (45%)	8 (36%)	22*
84	4 (17%)	15 (65%)	4 (17%)	23

*2 week 16 samples and 1 week 36 sample were lost in shipping and 1 week 72 sample was not collected due to an error; these are not counted as failures or successes.

ALT Normalization by Week for 17 Subjects with Elevated ALT at Entry

Week	N (%) > ULN	N (%) ≤ ULN	Total
2	15 (88%)	2 (12%)	17
4	11 (65%)	6 (35%)	17
8	9 (53%)	8 (47%)	15
12	8 (53%)	7 (47%)	15
14	4 (29%)	10 (71%)	14
16	4 (27%)	11 (73%)	15
20	2 (15%)	11 (85%)	13
24	2 (15%)	11 (85%)	13
30	4 (29%)	10 (71%)	14
36	4 (29%)	10 (71%)	14
42	8 (53%)	7 (47%)	15
48	5 (38%)	8 (62%)	13
54	6 (43%)	8 (57%)	14
60	6 (46%)	7 (54%)	13
72	6 (50%)	6 (50%)	12
84	9 (69%)	4 (31%)	13

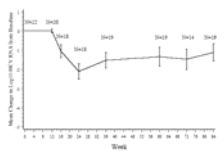
ULN = upper limit of normal

Overall Response (Undetectable HCV RNA *and* Normalized ALT)

Week	N (%) with Response	N (%) with No Response	Total
12	0 (0%)	23 (100%)	23
16	1 (5%)	21 (95%)	22*
24	4 (17%)	19 (83%)	23
36	3 (14%)	19 (86%)	22*
60	4 (17%)	19 (83%)	23
72	3 (14%)	19 (86%)	22*
84	3 (13%)	20 (87%)	23

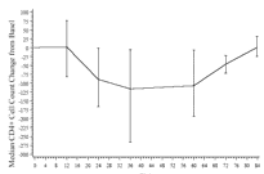
*Of 2 week 16 samples lost in shipping: 1 subject had normalized ALT and is not considered a failure or success at week 16, and 1 had an abnormal ALT and is considered a failure. One week 36 sample was lost in shipping: the subject had normalized ALT and is not counted as a failure or success at week 36. One week 72 sample was not collected due to error; the subject had a normal ALT level and is not considered a success or failure at week 72.

Mean Log_{10} HCV RNA Change from Baseline by Week*



*Bars represent standard errors

Median CD4+ Cell Count Change from Baseline*



*Bars represent interquartile range

CONCLUSIONS

•Low dose IL-2 plus PEG-IFN and RBV was associated with a high premature discontinuation rate

•Although this pilot study was not powered for efficacy, the end of treatment virologic response rate of 22% (95% CI 7 - 44%) and sustained virologic response rate of 17% (95% CI 5 - 39%) suggest that the treatment strategy does not enhance efficacy

•Our data do not support further study of the strategy of combining low dose daily IL-2 with PEG-IFN/RBV in larger clinical trials

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