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Pilot Study of Pioglitazone Prior to HCV Re-treatment in HIV/HCV Genotype 1-Infected Subjects with Insulin Resistance and Prior Nonresponse to Peginterferon and Ribavirin Therapy: A5239

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Abstract

Insulin resistance (IR) is associated with nonresponse to HCV treatment. In this multicenter, single-arm pilot study, adult, HIV/HCV genotype 1 coinfected prior nonresponders to peginterferon/ribavirin (PegIFN/RBV) with homeostatic model assessment-IR >2.5 were treated with pioglitazone(PIO) for 24 weeks followed by PegIFN/RBV/PIO. 3/19 subjects (15.8%) achieved undetectable HCV RNA at week 24 of PegIFN/RBV/PIO which was not significantly different than the historical null rate of 10% (p=0.29, lower limit of the exact 1-sided 90% confidence interval 5.9%). Over the 24 weeks of PIO monotherapy, ALT and AST declined significantly and correlated with improved metabolic parameters.

Keywords

hepatitis C; HIV; insulin resistance; pegylated interferon; nonresponder; metabolic

Introduction

Insulin resistance and its associated condition, fatty liver, occur commonly in HIV/HCV coinfected patients [1-10] and are associated with up to 50% poorer response rates to pegylated interferon alfa and ribavirin (PegIFN/RBV) treatment[1;11]. Mechansims by which HCV

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contributes to insulin resistance include both direct effects of viral proteins on insulin signaling and indirect effects of HCV-induced proinflammatory cytokines[12]. Pioglitazone (PIO) targets the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) receptor that controls the expression of insulin-sensitizing genes. Because the intracellular signaling pathways for insulin and interferon signaling overlap, it is plausible that improving insulin sensitivity could improve interferon responsiveness[12]. For these reasons, we hypothesized that treating insulin resistance with pioglitazone would improve virologic response rates to PegIFN/RBV retreatment. We also examined for beneficial effects of PIO monotherapy on liver and metabolic parameters.

Methods

Study Design

A5239 was a single-arm pilot study in which prior nonresponders to PegIFN/RBV with documented insulin resistance were treated with PIO prior to and during hepatitis C retreatment. Subjects received 24 weeks of PIO followed by continued PIO therapy plus PegIFN/RBV for 12-48 weeks depending on treatment response. The primary endpoint of the study was virologic response defined as HCV RNA below the limit of quantitative assay detection at week 24 of PegIFN/RBV/PIO treatment. This was chosen as the primary endpoint because neither null nor partial responders would have achieved this endpoint during their prior HCV treatment course. Subjects were also evaluated for sustained virologic response (SVR) 24 weeks after completion of PegIFN/RBV/PIO.

Eligibility Criteria

The study population was HIV-1/HCV genotype 1-infected adults with insulin resistance and non-response to previous treatment with PegIFN alfa-2a 180 mcg/week, or alfa-2b 1.5 mcg/kg/week, and ≥1000 mg/day RBV given for at least 12 consecutive weeks. Prior nonresponse status was defined as: prior null responder with <2 $\log_{10}$ drop in HCV RNA from pretreatment levels AND detectable HCV RNA by RT-PCR or bDNA assay after ≥10 weeks and <22 weeks of therapy OR prior partial responder with detectable HCV RNA by RT-PCR or bDNA assay after ≥22 weeks and <30 weeks of therapy, not attributable to nonadherence or dose reductions. Relapsers were excluded. Insulin resistance was defined as homeostatic model assessment of insulin resistance (HOMA-IR) value of >2.5 (calculated as fasting serum insulin (μU/mL) x fasting plasma glucose (mg/dL)/405), consistent with many other studies of insulin resistance and HCV treatment[1;2;11;13-15]. Subjects with diabetes, fasting plasma glucose ≥126 mg/dL, or on antidiabetic medications were excluded.

Subjects were required to have $CD4^+$ cell counts ≥200 cells/μL, no active opportunistic infections, no antiretroviral therapy (ART) or stable ART that did not include zidovudine or didanosine for at least 12 weeks prior to study entry. Subjects with renal insufficiency, significant anemia, decompensated cirrhosis, chronic hepatitis B, other liver disease (besides nonalcoholic fatty liver disease), or other contraindications to treatment with peginterferon/ribavirin were excluded.

Informed consent was obtained from subjects. Human experimentation guidelines of the United States Department of Health and Human Services and those of the study sites' institutions were followed in the conduct of this study.

Study Treatment

All subjects received at least 24 weeks of PIO 30 mg/day prior to PegIFN/RBV. Management for hepatotoxicity was prespecified based on elevations in transaminases, bilirubin, or signs of hepatic decompensation. PegIFN alfa-2a (Pegasys™; Roche (Genentech)) was dosed at 180 mcg/week. Ribavirin (Copegus™; Roche(Genentech)) dose was weight-based, with doses of 1000(<75 kg) or 1200mg/day(≥75 kg) divided twice daily. PegIFN and RBV doses were reduced if prespecified toxicity criteria were met. Dose escalation was permitted if toxicities resolved. Concurrent use of growth factors was permitted for neutropenia and anemia. Stopping rules for treatment futility were applied including <2 $\log_{10}$ drop in HCV RNA after 12 weeks or detectable HCV RNA after 24 weeks of PegIFN/RBV/PIO.

Study Evaluations

Subjects were evaluated for adverse events and safety laboratory tests (including hepatic function panels) during PIO monotherapy (Weeks 2, 4, 8, 12, 18, 24) and during PegIFN/RBV/PIO (weeks 2, 4, 8, 12, 16, 24, 32, 40, 48). HCV viremia was assessed at a central lab by quantitative real-time PCR (Roche COBAS Amplicor v 2.0) at entry, PIO week 24, and PIO/PegIFN/RBV weeks 4, 12, 24, 48, 72 (lower level of quantification was 43 IU/mL). Fasting insulin, glucose, leptin, adiponectin, and cholesterol levels were performed at entry, PIO weeks 12, 24, and PIO/PegIFN/RBV weeks 12, 24, 48, 72. Oral glucose tolerance tests (OGTT) were performed at entry and PIO week 24. All metabolic testing aside from routine fasting glucose levels was performed centrally on stored specimens (Quest Diagnostics, Baltimore, MD): adiponectin by ELISA with coefficient of variation (CV) 3.3-7.3%(B-Bridge International, Sunnyvale, CA), insulin by enzyme-based chemiluminescent immunometric assay with CV 3.7%-7.3% (Siemens Healthcare Diagnostics, Deerfield, IL), leptin by electrochmiluminescence with CV 7.8%-12.0% (Nichols Institute, San Juan Capsitrano, CA).

Statistical Methods

The primary endpoint was virologic response defined as undetectable HCV RNA at week 24 of PIO/PegIFN/RBV treatment. Secondary endpoints included SVR, safety endpoints, and changes in metabolic parameters and transaminase levels during PIO monotherapy.

The study was powered to detect a week 24 response rate of at least 30% which was the minimum response felt to be meaningful in terms of further pursuing this strategy. Based on this response rate and using a one-sided type I error of 10%, a sample size of 30 subjects allowed 90% power to detect a significant increase from a historical null rate (at week 24 of retreatment) of 10%. The relaxed type I error of 10% was used to allow for high power for detection of a positive effect with the plan to confirm a positive finding with a larger study.

All analyses were conducted as intent-to-treat. For virologic response rates, an exact test of proportions (and corresponding lower limit of the one-sided 90% CI) was used. For change in continuous endpoints, a two-sided Wilcoxon signed rank test was used to assess if the changes were significantly different than zero. P-values <0.10 were deemed statistically significant, and nominal values are reported without adjustment for multiple comparisons. Analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC) and StatXact, version 9.0 (Cytel Inc., Cambridge, MA).

Results

The study accrued 19 of the planned 30 subjects between March 2009 and November 2010 before being closed due to slow accrual. The majority of the 31 subjects who failed screening were excluded for HOMA-IR ≤2.5. Of enrolled subjects, 84% were male, 47% were black non-Hispanic, 11% were Hispanic and 42% were white non-Hispanic. Thirteen were prior null responders while 6 were partial responders. All but one participant was on ART (10 were on protease inhibitor-based and 8 NNRTI-based regimens; no regimens included stavudine), median CD4 was 532 cells/ μL and 79% had HIV RNA <50 copies/ml. Their median BMI was 27.7, median HOMA-IR was 4.5, and 89% had HCV RNA levels ≥ 1,000,000 IU/mL.

HCV Virologic Responses

Of the 19 subjects, 3 (15.8 %) achieved undetectable HCV RNA at week 24 of PIO/PegIFN/RBV, which did not differ significantly from the historical null rate of 10% (p=0.29, lower limit of the exact 1-sided 90% CI = 5.9%). Of the 3 subjects who were below detection at week 24, 1 had virologic relapse post treatment, 1 was lost to follow up, and 1 subject had an SVR. Of the other 16 subjects, 3 discontinued during PIO monotherapy (1 abnormal liver tests, 2 other reasons), 1 was lost to follow up, and 12 met the study defined criteria for virologic nonresponse at week 12 (10 subjects) or 24 (2 subjects).

Safety

Grade 3 ALT elevations were reported in 3 subjects during PIO monotherapy. PIO was continued in one, held in one, and discontinued in the other. There were no reports of hepatic decompensation. Two other grade 3 adverse events (lipase and phosphorus) and two Grade 4 events (lipase and neutropenia) occurred during PIO monotherapy. There was a slight decline in hemoglobin levels (median decrease 0.3 g/dL, p=0.14) and increase in weight (median increase 1.6 kg, p=0.21) during PIO monotherapy.

Effects of PIO monotherapy

Over the 24 weeks of PIO monotherapy, statistically significant declines in ALT and AST occurred (Figure 1). No significant changes in HCV RNA, bilirubin or GGT were observed. Table 1 shows metabolic outcomes of PIO monotherapy. Statistically significant increases in adiponectin and decreases in fasting insulin, HOMA-IR, and glucose area under the curve during OGTT were observed. Leptin and cholesterol levels did not change significantly. The decline in ALT correlated with change in HOMA-IR (Spearman's r =0.609, p = 0.012), fasting glucose (r=0.521, p=0.038), fasting insulin (r=0.624, p=0.010), and insulin AUC

(r=0.610, p=0.027). The decline in AST correlated with change in leptin and fasting glucose levels (r=0.492 , p=0.053 and r=0.563 , p=0.023, respectively).

Discussion

Despite recent advances in HCV therapy, the treatment of prior PegIFN/RBV nonresponders remains challenging. Given the association between insulin resistance (IR) and nonresponse to HCV treatment, we hypothesized that PIO would enhance interferon responsiveness and improve virologic response rates during PegIFN/RBV retreatment of HCV in HIV-infected subjects with IR. After pretreatment with PIO, 3 of 19 subjects achieved undetectable HCV RNA at week 24 of PegIFN/RBV/PIO, of which. only 1 achieved an SVR. Thus, there was no signal to suggest that PIO enhanced treatment response rates in this patient population.

Others have examined whether targeting insulin resistance improves HCV treatment outcomes in HIV-uninfected persons with both positive[13;16] and negative results[14;15;17]. The only other such published study of nonresponders, a single arm, multicenter study designed to look at PIO given simultaneously with initiation of HCV retreatment, was terminated early after the first 5 subjects had unsatisfactory virologic responses at week 12[15]. Notably, that study dosed PIO at only 15 mg daily, and 2 of the 5 subjects demonstrated worsened IR at week 12. More data exist regarding the use of this strategy in HCV treatment-naïve populations. Two prospective randomized, controlled studies investigated the addition of PIO to PegIFN/RBV therapy in HIV-uninfected, HCV-infected patients undergoing their initial course of PegIFN/RBV. The first included HCV genotype 4 subjects and demonstrated improved on-treatment response and SVR rates in patients randomized to PIO compared to placebo (rapid virologic response 27% vs. 6% and SVR 60% vs. 39%, respectively)[16]. In the other study which included subjects with HCV genotype 1, PIO improved IR but did not improve on-treatment response or SVR rates (SVR 41% PIO vs. 57% no PIO)[14]. Both studies used PIO doses of at least 30 mg, however PIO was started concurrently with HCV therapy in the study of genotype 4 subjects and 16 weeks prior to HCV treatment in the genotype 1 study. Differences in regimen (e.g. insulin-sensitizing agent, dosage, simultaneous versus insulin-sensitizing agent first), definition of insulin resistance, HCV genotype, study population (e.g. HCV treatment experience status), and efficacy of improving IR may account for the variability of responses in these and other studies.

Our study had several important limitations, including its single arm design, small sample size and under enrollment. Nonetheless, while we did not show improvement in virologic response, we did show a significant improvement in serum aminotransferase levels during PIO monotherapy that correlated with improvements in metabolic parameters. Given that HCV RNA levels did not decline during PIO monotherapy, the improvement in AST and ALT levels may relate to reduced necroinflammation in the liver, such as that described in studies of PIO for nonalcoholic steatohepatitis (NASH) treatment[18;19]. While histopathologic evaluation of the liver was not performed in this study, past studies of PIO for NASH have demonstrated histologic improvement including reduced steatosis as well lobular inflammation and ballooning necrosis[18;19]. In addition to improved histology and aminotransferase levels, these studies of NASH also showed improvements in metabolic

parameters such as HOMA-IR and adiponectin levels, similar to what we observed. Our study is the first to demonstrate this effect of PIO in improving laboratory markers of liver necroinflammation in HIV-infected individuals with HCV and IR. While safety considerations have emerged for thiazolidinediones like PIO , selective PPAR-gamma modulators in development with potentially superior safety profiles beckon future study of this finding.

In summary, treating insulin resistance with PIO prior to and during HCV retreatment in prior nonresponders did not produce a week 24 response or SVR rate sufficient to justify using this approach routinely but has not ruled out its potential utility in select populations. Decreases in serum aminotransferase levels and improvements in metabolic parameters were observed during PIO monotherapy. Since insulin resistance and fatty liver occur commonly in both HIV/HCV coinfected and HIV-monoinfected patients, therapies targeting PPAR-gamma or other strategies for improving insulin sensitivity warrant further investigation.

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Potential conflict of interest

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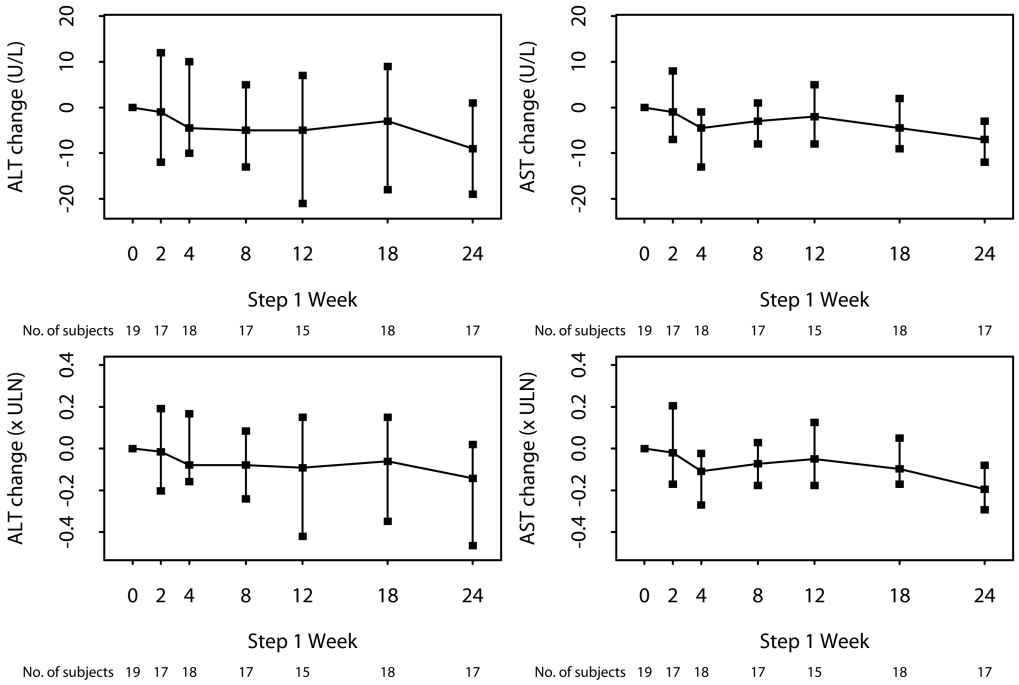

Figure 1.

Change in Transaminase Levels during Pioglitazone Monotherapy; Median (Q1,Q3) Legend: Statistically significant declines in ALT and AST (expressed as absolute values (top boxes) and a ratio to the upper limit of normal (ULN) (bottom boxes)) occurred after the 24 week course of pioglitazone monotherapy. The statistical analysis was conducted using the ratio to ULN, since these were run at local labs with varying normal ranges [median (Q1,Q3) −0.14 (−0.47, 0.02) × ULN (p=0.031) and −0.20 (−0.29, −0.08) × ULN (p=0.018), respectively].

Table 1

Change in Hemoglobin, Liver-Related Tests and Metabolic Tests Observed During Pioglitazone Monotherapy

N=19[a]	**Baseline median (Q1,Q3)**	**Change during PIO median (Q1,Q3)**	**P value**
Hemoglobin (g/dL)	14.3 (11.6,16.7)	−0.30 (−0.7,0)	0.140
ALT (U/L)	**58 (43,74)**	**−9 (−19,1)**	
(× ULN)[b]	**1.15 (0.92,1.37)**	**−0.14 (−0.47, 0.02)**	**0.031**
AST (U/L)	**50 (44,60)**	**−7 (−12, −3)**	
(× ULN)[b]	**1.24 (1.09,1.51)**	**−0.20 (−0.29,−0.08)**	**0.018**
GGT (IU/L)	130 (52,247)	−20 (−67,14)	0.46
HCV RNA (log_{10} IU/ml)	6.67 (6.46,6.92)	0.20 (−0.09,0.35)	0.17
Fasting Glucose (mg/dL)	106 (94,113)	−5.5 (−8,2.5)	0.19
Fasting Insulin (uIU/ml)[c]	**18.5 (13.5,26)**	**−5.5 (−14.5,4.5)**	**0.073**
Glucose AUC (mg/dL/min)	136 (122,177)	−7.3 (−11.8,4.5)	0.095
Insulin AUC (uIU/ml/min)[c]	91 (58,144)	−26 (−73,17)	0.20
HOMA-IR[c]	**4.5 (3,6)**	−1.4 (−4.1,0.9)	0.055
Total cholesterol (mg/dL)	153 (118,178)	5.5 (−2.0,20.5)	0.27
HDL cholesterol (mg/dL)	34 (23,102)	1.5 (−2.5,5.5)	0.45
Triglycerides (mg/dL)	161 (50,350)	28.5 (−15.5,73.0)	0.11
Adiponectin (ng/mL)	**5 (3,9)**	**4.5 (2,8)**	**<0.001**
Leptin (ng/mL)	7.3 (2.8,11.2)	−0.4 (−1.1,0.5)	0.30
Weight (kg)	83.7 (70.8,98.8)	1.6 (−0.5,2.5)	0.21

[a] Number of subjects with available results (Week 0, Week 24): hemoglobin (19,17), ALT (19,19), AST (19,17), GGT (14,11), HCV RNA (19,17) fasting glucose (19,16), glucose AUC (18,16), fasting insulin (19,15), insulin AUC (18,13), HOMA-IR (19,15), cholesterol, triglycerides, adiponectin, leptin and weight (18,16).

[b] ALT and AST were expressed as a ratio to the upper limit for statistical analsyses since these were run at local labs with varying normal ranges.

[c] Fasting insulin levels >300 uUI/ml (the upper limit) were interpreted as 300. One subject had a week 24 fasting insulin level considered to not be consistent with fasting. This measurement was excluded in the analyses shown here.