Twice-weekly pegylated interferon-α-2a and ribavirin results in superior viral kinetics in HIV/hepatitis C virus co-infected patients compared to standard therapy


Background: Hepatitis C virus (HCV)/HIV co-infected patients have more rapid progression of liver fibrosis and only modest cure rates (sustained virologic responses, SVRs) when compared to HCV monoinfected patients.

Method: We compared the virologic responses of either twice-weekly peginterferon-α-2a 180 µg/week (for 4 weeks, followed by weekly dosing) or weekly peginterferon-α-2a 180 µg/week, and weight-based ribavirin (1–1.2 g/day), among HIV/HCV co-infected genotype-1 individuals.

Results: Patients receiving the investigational dosing had lower levels of HCV RNA at all time points after initiation of therapy. More patients on this arm achieved clinically relevant early virological responses at weeks 1, 2, 4, 12, and 24. The enhanced early virologic response observed with the investigational arm was associated with a higher induction of interferon-stimulated genes. This early double dose regimen also resulted in a rapid normalization of liver enzymes. Twice-weekly peginterferon-α-2a was associated with more frequent early virological responses with similar safety profiles when compared with standard therapy.

Conclusion: Our results, when confirmed in larger randomized clinical trials, may provide a novel therapeutic approach to improve SVR among HIV/HCV co-infected patients, especially African–American patients.

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Introduction

Hepatitis C virus (HCV) co-infection occurs approximately in one-third of all patients infected with HIV in the United States [1]. Although the successful implementation of antiretroviral therapy (ART) has dramatically decreased the number of AIDS-related opportunistic infections, morbidity and mortality rates related to...
HCV-related liver disease have increased in this group [2–4]. In comparison to HCV monoinfected patients, HIV/HCV co-infected patients have an accelerated progression of liver disease [5] and only attain modest cure rates with treatment of pegylated interferon (peg-IFN) and ribavirin [6–11]. Along with significant associated toxicities, the standard treatment of peg-IFN and ribavirin yields only low rates of sustained virological response (SVR) among HIV/HCV co-infected genotype 1 patients. Furthermore, African-Americans have poor viral kinetics, pharmacodynamics, and SVR rates in comparison to whites, but constitute a significant proportion of all HIV/HCV co-infected individuals [9,12,13]. This warrants the development of novel therapeutic regimens to improve SVR in this difficult-to-treat population [7,10,11].

Early HCV viral kinetics have shown a strong predictive ability for SVR in HIV/HCV co-infected patients [14], and improvements in early viral kinetics could potentially translate into higher rates of SVR. Recent studies on early HCV kinetics in HIV/HCV co-infected patients show that almost 90% of patients treated with peg-IFN α-2b and ribavirin experienced an end of the week rebound consistent with a decline in serum IFN levels [14–17]. A large, randomized controlled trial of 896 patients attempted to overcome the end of the week rebound with high-induction dosing of peg-IFN and ribavirin at the beginning of each week [18]. Although this high-dose peg-IFN enhanced early virologic response rates, SVR rates were not significantly improved [18–20]. A better alternative approach to induction dosing is twice-weekly dosing of peg-IFN. The additional dose of peg-IFN is given as serum IFN levels begin to decline, which may prevent an end of the week rebound [12]. Studies of HCV viral kinetics in HCV monoinfected patients have suggested the use of twice-weekly peg-IFN to improve early HCV kinetics and subsequently enhance SVR rates [21]. These studies suggest that a twice-weekly dosing of peg-IFN could prevent an end of the week rebound, improve the early virological response (EVR), and potentially increase SVR among HIV/HCV co-infected individuals.

In this study, we treated HIV/HCV genotype 1 co-infected patients with weekly or twice-weekly peg-IFN for 4 weeks, followed by once weekly peg-IFN and standard doses of ribavirin for a total of 48 weeks. We evaluated viral kinetics, biochemical responses, and adverse events in order to compare safety, tolerability, and early virological efficacy.

**Materials and methods**

**Study design**

This was a pilot, prospective, randomized controlled trial performed at the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) in Bethesda, Maryland from 2004 to 2007. Nineteen HIV/HCV genotype-1 co-infected patients were randomized to receive either standard or investigational therapy. Ten patients on the standard arm received peg-IFN–α-2a at 180 µg subcutaneously every week (Pegasys; Hoffman La-Roche Inc., Nutley, New Jersey, USA) and ribavirin daily (Copegus; Hoffman La-Roche Inc.) at 400 mg every morning (qam) and 600 mg every evening (qpm) for less than 75 kg, and 600 mg twice per day for more than 75 kg for 48 weeks and followed up for 24 weeks after the end of treatment. Nine patients on the investigational arm received peg-IFN–α-2a at 180 µg twice weekly for 4 weeks (second dose given on day 4), followed by a once weekly regimen for 44 weeks along with ribavirin for 48 weeks and followed up for 24 weeks after the end of treatment for SVR. All patients signed informed consent approved by the NIAID Institutional Review Board prior to enrollment in the study. The primary end point of the study was the change in HCV viral load at day 7 and the sample size was calculated to meet this end point.

**Laboratory studies**

HCV and HIV RNA concentration in plasma were measured by VERSANT RNA 3.0 assay (Bayer Diagnostics, Puteaux, France). HCV RNA concentration was measured in plasma on day 0, 3, 5, 6, 7, 10, 14, 21, 28, 42, 56, and then every 4 weeks for 72 weeks. Liver chemistry and safety laboratory tests were performed prior to treatment and at each study visit.

A rapid virologic response (RVR) by week 4 is defined as HCV RNA levels below the limit of detection at the end of 4 weeks of treatment. EVR was defined as at least 2-log drop in HCV RNA levels within 12 weeks after initiation of therapy. End of treatment response (ETR) was defined as HCV RNA levels below the limit of detection at the end of 48 weeks of treatment. SVR was defined as HCV RNA levels below the limit of detection 24 weeks after the end of treatment.

**Study participants**

Patients were eligible for the study if they were more than 18 years of age, had CD4+ T-cell counts more than 100 cells/µl, absolute neutrophil counts more than 1000 cells/µl, HCV genotype-1 viral load more than 2000 copies/ml, histologic evidence of chronic hepatitis C on liver biopsy, and stable HIV disease with or without ART (in accordance with Department of Health and Human Services guidelines) with exclusion criteria described previously (Supplemental Table 1, http://links.lww.com/QAD/A135) [12,28].
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detecting the expression of 35 genes previously described [22].

Measurement of serum pegylated interferon-α-2a concentrations
Peg-IFN-α-2a concentrations were measured at days 0, 1, 3, 5, 7, 10, 14, 21, 28, 42, 56, and 84 by applying a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) method (Bender MedSystems Diagnostics GmbH, Vienna, Austria) previously described [12].

Modeling viral kinetics, pharmacokinetics, and pharmacodynamics
Clinical pharmacokinetic and viral kinetic data of each individual patient were fitted with a full pharmacokinetic–pharmacodynamic model. The model mainly follows the approach described in the study by Shudo et al. [23]. Pharmacokinetics of peg-IFN was modeled by a Bateman function using parameters $k_a$ and $k_e$ for drug absorption and elimination, respectively, as well as $FD/V_d$ for the bioavailable drug $FD$ when administered with dose $D$ divided by the volume of distribution $V_d$. The link to the pharmacodynamic model was done by assuming that the effect of blocking viral production depends on drug levels of IFN $C(t)$ through the Hill function

$$
e(t) = \frac{C(t)^h}{C(t)^h + IC_{50}^h}
$$

where $h$ describes the Hill slope and $IC_{50}$, the drug level that blocks the viral production by 50%. As the antiviral efficacy $e$ depends on peg-IFN drug levels and, therefore, varies with time, we can use mean and maximum efficacy as summarizing measures for the efficacy of antiviral treatment. The viral kinetic model is described by the differential equation system

$$V(t) = (1 - e)(1 - \rho) p_I(t) - c V(t)$$

$$V_d(t) = (1 - e) \rho p_I(t) - c V(t)$$

$$\dot{I}(t) = \beta T(t) V(t) + p_I I(t) \left(1 - \frac{T(t) + I(t)}{T(0) + I(0)}\right) - \delta I(t)$$

$$\dot{T}(t) = \gamma \left(1 - \frac{T(t) + I(t)}{T(0) + I(0)}\right)
$$

which is based on the general model for hepatitis C viral kinetics [23]. It includes a proliferation of infected cells compartment $I$ with rate $p_I$ as in the study by Dahari et al. [24] and a simple linear differential equation function for the infectable target cells compartment $T$, which accounts for the regenerative power of the liver [25]. Further parameters describing the dynamics of the viral load compartment and the infected cells compartment are $\rho$ describing the antiviral effect of ribavirin to split the newly produced virus in infectable and uninfectable virus ($V_d$ and $V_u$, respectively) as in the study by Dixit et al. [26]; $p$ describing the viral production rate in the untreated chronic patient; $c$ describing viral clearance; and $\delta$

describing infected cell loss. Two patients on standard treatment showed a nonresponse to IFN and no decline during the first 4 weeks. In these patients, no viral kinetic modeling could be performed.

Statistical analyses
We fitted the pharmacokinetic and the logarithmized viral kinetic model function to individual patient data by a maximum likelihood approach. We estimate the pharmacokinetic, viral kinetic parameters $k_e$, the elimination rate of peg-IFN, $F/V_d$ the ratio between bioavailability, the volume of distribution, $IC_{50}$ that is most important in determining the individual antiviral efficacy, the Hill coefficient $h$, the infected cell loss rate $\delta$, and the steady state viral load $V(0)$. Further parameters were fixed because observations were not frequent enough to allow for a reliable estimation. We used an absorption rate of peg-IFN of $k_a = 2$ per day, a viral clearance rate of $c = 5$ per day, an effect of ribavirin on the production of noninfectious virus as $\rho = 0.8$, a regeneration rate of the compartment of uninfected target cells of $\gamma = 3$ per day, a proliferation rate of $p_I = 3$ per day, and $T(0)/I(0) = 1$.

These are reasonable and biologically plausible values found in previous viral kinetic analysis. Furthermore, sensitivity analysis shows that these parameters are of minor influence.

The nonparametric Wilcoxon–Mann–Whitney $U$-test was used to determine the differences between the treatment groups. The Wilcoxon rank sum test was used to determine absolute viral load changes from baseline, and Fisher’s exact test was used to determine the differences between adverse events and alanine aminotransferase (ALT), aspartate aminotransferase (AST), and interferon-stimulated gene (ISG) changes between the two groups.

Results

Investigational therapy yields better early virologic response
The baseline demographics of the 19 patients participating in this study are shown in Supplemental Table 1, http://links.lww.com/QAD/A135. The patient population was predominantly men (84%) and African–American (58%) with a median CD4+ T-cell count of 483 cells/µL. All patients were co-infected with HIV and HCV genotype 1. Four patients (two receiving investigational therapy and two receiving standard therapy) stopped treatment early at weeks 3, 4, 10, and 32 due to adverse events.

All 19 patients met the primary end point, which was the change in HCV RNA levels on day 7 between the two groups. Patients who received investigational therapy had a significantly lower HCV viral load on day 7 [median
log_{10} HCV RNA 3.61 (range <2.79–6.11) compared to those who were randomized to receive standard therapy [median log_{10} HCV RNA 5.59 (range 4.65–6.40); P = 0.032]. Furthermore, patients who received investigational therapy showed a significantly larger decline in HCV viral load than the standard therapy during the first week (median log_{10} HCV RNA decline 1.28 vs. 0.17; P = 0.018; Fig. 1a).

Patients on the investigational arm experienced a steeper first phase decline than patients on the standard arm (Fig. 1a). Other early virological end points (Fig. 1b) also showed that more patients receiving investigational therapy achieved relevant on-treatment virological response defined as at least 2-log drop in HCV viral load from baseline by week 2 (44 vs. 0%), week 4 (63 vs. 40%), and week 12 (71 vs. 50%). Clinical end points were week 4 RVR (63 vs. 30%), EVR (63 vs. 44%), week 48 ETR (57 vs. 63%), and week 72 SVR (57 vs. 50%; Fig. 1c). Although all early virologic response parameters were superior in patients receiving investigational therapy, these differences did not reach statistical significance given the small sample size.

**HIV/hepatitis C virus co-infected African–Americans have improved viral kinetics on investigational therapy**

A subset analysis of African–Americans, who represent the major group of patients who poorly respond to standard therapy, was performed. In HIV/HCV genotype-1 co-infected African–American patients, a significantly faster viral load decline at day 7 was observed in patients receiving investigational in comparison to those receiving standard therapy (median log_{10} HCV RNA 1.67 vs. 0.04, P = 0.009; Fig. 1d). Most early virologic parameters were more favorable in African–Americans receiving investigational therapy compared to those receiving standard therapy, such as at least 2-log drop...
in HCV viral load from baseline by week 2 (60 vs. 0%) and RVR (75 vs. 0%; P < 0.05). Thus, investigational therapy was most beneficial in African–Americans who represent the most difficult-to-treat subgroup in the HIV/HCV co-infected patients.

Pharmacokinetic and viral kinetic modeling
We fitted a full pharmacokinetic and viral kinetic model for the data of the first 6 weeks. Interestingly, dose-independent pharmacokinetic parameters as the elimination rate were similar between the investigational group and the standard treatment group, but trough levels of IFN from the pharmacokinetic fit were significantly larger for bi-weekly dosing (Table 1 and Fig. 2, at day 7: P = 0.011). Differences in pharmacokinetics between African–American and other patients were small (P > 0.2 for the pharmacokinetic parameters).

Viral kinetic analysis showed comparable Hill coefficients and IC50 levels between the investigational treatment group and the standard treatment group (Table 1). Nevertheless, significantly higher mean and maximum efficiency were observed in the investigational group (Table 1, P = 0.046 and 0.038, respectively). Once bi-weekly dosing ended after week 4, the advantage in treatment efficiency in the investigational group was lost, and viral kinetics became slower (Fig. 2 a and c).

Interferon-stimulated gene expression
Our previous studies have demonstrated that induction of ISGs is a major biological correlate of antiviral efficacy of IFN-based anti-HCV therapy. We investigated whether the enhanced antiviral effect observed with the investigational therapy was associated with similar levels of induction of ISG. As anticipated, the additional bi-weekly dosing of peg-IFN significantly increased the expression of ISG in all patients receiving investigational therapy from baseline when compared to that observed with standard therapy (Fig. 3a). Additionally, patients who attained SVR were able to induce significantly higher levels of ISG than nonresponders whether they received standard or investigational therapy. These results suggest that induction of ISG is an important surrogate biomarker of therapeutic response to IFN-based anti-HCV treatment regimens.

Investigational therapy results in earlier normalization of liver enzymes
Normalization of serum levels of ALT and AST are indicators of HCV clearance and subsequent reduction in hepatic inflammation. At baseline, all but four patients had elevated ALT and AST levels, which were not significantly different at baseline between the treatment groups. Patients with elevated hepatic enzymes at baseline undergoing investigational dosing normalized hepatic enzymes quicker than patients on standard therapy (Fig. 3b). ALT levels at week 24 and at the end of treatment were significantly lower in the investigational group than in the standard treatment group. Thus, investigational therapy normalizes liver enzymes much earlier than standard therapy, suggesting earlier clearance of HCV from infected hepatocytes.

Investigational therapy is safe and well tolerated in HIV/hepatitis C virus co-infected individuals
In this study, the investigational therapy was equally well tolerated as standard therapy in HIV/HCV genotype-1 co-infected individuals. The overall incidence of adverse events was similar in both groups (P > 0.05), with no significant differences in quantity or grade of adverse events (Fig. 4a). The rates of adverse events such as hemoglobin level less than 12 g/dl was 30 vs. 44% (P > 0.05) or absolute neutrophil count less than 1000 cells/μl was 20 vs. 33% (P > 0.05) in standard vs. investigational arms respectively (Fig. 4b). Both groups experienced a decline in CD4+ T-cell counts (median decline of 78 vs. 51 cells/μl in the standard arm vs. investigational arm by week 6, (P > 0.20; Fig. 4c), but the CD4+ T-cell percentage remained unchanged (30 vs. 31%, P > 0.20). Although both groups experienced adverse events commonly associated with IFN-based therapy, the investigational group did not demonstrate significantly more toxicities, which suggests that the biweekly therapy is safe and as equally well tolerated as standard therapy.

Discussion
Our study suggests that twice-weekly peg-IFN-α-2a for 4 weeks followed by weekly dosing and ribavirin has a
A superior early virologic response compared with the standard therapy of weekly peg-IFN-α-2a and ribavirin among HIV/HCV co-infected genotype 1 individuals, particularly among African–Americans. More patients receiving investigational therapy met early virologic end points than those receiving standard therapy and did not report a significantly higher number of adverse events. Mathematical modeling suggests the improved early virologic response was associated with a successful prevention of viral rebound at the end of the week and an increased efficacy of the investigational therapy compared with standard therapy. Host genomic analysis indicates the ability to induce ISG as a major potential mechanism for the observed virologic response. Thus, the superior viral kinetics, pharmacokinetics, pharmacodynamics, and enhanced ISG induction of the investigational therapy were observed.

**Fig. 2.** Viral kinetics, pharmacokinetics, and pharmacodynamics as response to standard vs. investigational therapy. Mean fitted curves for hepatitis C viral kinetics (a and b), pharmacokinetics (c and d), and pharmacodynamics (e and f) in the investigational arm compared with the standard arm. Mean fitted curves are plotted (a, c, f) as a function of therapeutic regimen (red lines for the standard treatment arm and blue lines for the investigational treatment arm) and (b, d, f) as a function of race (solid lines for African–Americans and dashed lines for Caucasians or Hispanics).
treatment arm illustrate the potential significance of this viral kinetics-driven therapy for eradicating HCV in this difficult-to-treat patient population.

Although previous studies have attempted to improve early viral kinetics via high-dose peg-IFN-α-2a induction therapy, our study uniquely targeted the end of the week viral rebound with twice-weekly dosing of peg-IFN-α-2a. By administering an additional dose of peg-IFN-α-2a midweek as serum IFN levels begin to decline and HCV viral load correspondingly increases, a more rapid decline in HCV viral load was observed in patients receiving investigational therapy. Furthermore, a subset analysis of African–American patients demonstrated that the investigational therapy significantly benefited this group. As previously suggested, improving early viral kinetics may be essential in developing more effective anti-HCV therapies as early viral kinetics are important predictors of long-term virologic outcomes [28].

In order to understand the antiviral effect of peg-IFN-α-2a in weekly and bi-weekly dosing, we modeled viral kinetic, pharmacokinetic, and pharmacodynamic parameters based upon treatment as well as race. Pharmacokinetic modeling not only confirmed that trough serum IFN levels were increased by bi-weekly dosing during the first 4 weeks, but maximum serum IFN levels remain equal or are only moderately increased. After stopping bi-weekly dosing, subsequently, the pharmacokinetic profile normalized. Though patients on the investigational arm only received increased IFN for the first 4 weeks of therapy, the viral kinetics were significantly improved in the investigational therapy and HCV viral levels were already below the level of detection in most patients. Again by improving early viral kinetics, the investigational therapy attained more early virologic responses that prior studies have shown to be predictive of achieving SVR. This improved antiviral response in the investigational arm can also be confirmed by pharmacodynamic modeling. The mean estimated efficiency of blocking viral production is significantly higher in the investigational arm during the bi-weekly dosing phase. In a subset analysis, these effects were improved among African–Americans. Hence, this viral

Fig. 3. Interferon-stimulated gene expression and liver enzyme normalization. (a) Interferon-stimulated gene (ISG) expression as a function of treatment arm and therapeutic response. ISG expression at baseline and during treatment by treatment arm and therapeutic response. The specific ISGs analyzed at baseline and week 4 were EIF2AK2, G1P3, IFI27, IFI44, IFIT1, IFIT3, IFITM1, IFITM3, IRF7, ISG15, ISG20, LY6E, MX1, MX2, OAS1, OAS2, PLSCR1, PPIA, SP110, and STAT1. (b) Liver enzyme normalization. More patients with elevated hepatic enzymes undergoing investigational therapy normalized hepatic enzymes than patients with elevated hepatic enzymes on standard therapy.

Fig. 4. Adverse events profile. (a) Treatment-related toxicities. The adverse event profiles were similar between the two groups. No statistically higher incidences of adverse events were observed in the more common incidences involving patients with anemia (hemoglobin level <12 g/dl), neutropenia, or psychiatric toxicity. (b) CD4 cell decline over time. Both groups experienced a decline in CD4⁺ T-cell counts, but maintained comparable CD4⁺ levels throughout the standard and investigational therapy.
kinetics-driven clinical strategy would appear to benefit the patient population who are least responsive to the current standard of care.

While data from this pilot study showed an increased antiviral efficacy of the investigational regimen, this study also showed the safety and tolerability of twice-weekly dosing. Combination therapy for HCV with peg-IFN-α-2a and ribavirin is associated with many serious dose-limiting adverse events, ranging from fatigue, headache, nausea, insomnia, pyrexia, anemia, myalgia, neutropenia, and depression to severe hematological disorders [29]. Conceivably, increasing the frequency of peg-IFN-α-2a in the first 4 weeks could result in increased rates of adverse events and study discontinuation rates; however, statistical analysis showed no significant differences between patients in both groups. Although many patients experienced adverse events, these were easily manageable. Patients receiving investigational therapy also had a faster normalization of hepatic enzymes, indicating an earlier more rapid clearance of HCV from infected hepatocytes and reversal of ongoing hepatic parenchymal damage. These results suggest that twice-weekly peg-IFN-α-2a with ribavirin was well tolerated, safe, and resulted in improved virologic and biochemical response when compared to the standard therapy among HIV/HCV co-infected individuals.

Previous DNA microarray studies examining the baseline expression of ISG have demonstrated that nonresponders exhibit significantly higher levels of baseline ISG expression than responders [27,30,31]. Moreover, patients with high baseline levels of ISG do not induce higher levels of ISG expression during IFN therapy, whereas those who achieve SVR do induce ISG after IFN therapy [27,30,31]. These studies suggest that elevated endogenous IFN expression potentially accounts for the refractoriness of immune cells to exogenous IFN therapy in nonresponders, and these patients have an increased threshold for antiviral effect with IFN-based therapy for HCV. Our results are consistent with earlier findings that nonresponders to combination therapy have slower viral kinetics and pharmacodynamic parameters that suggest a greater refractoriness to IFN therapy. Therefore, increasing the frequency of IFN dosing may overcome this mechanism of treatment failure by inducing higher levels of ISG expression. Patients in this study who attained SVR induced significantly higher levels of ISG expression in comparison to nonresponders. In addition, our study demonstrates the effectiveness of twice-weekly peg-IFN-α-2a dosing in IFN induction, as all patients receiving investigational therapy induced significantly higher levels of ISG in comparison to patients receiving standard therapy. These combined results of enhanced ISG induction and superior early virologic responses of the bi-weekly dosing of peg-IFN-α-2a therapy further suggest the induction of ISG as an important biological correlate of antiviral efficacy of IFN-based anti-HCV treatment, especially with twice-weekly peg-IFN-α-2a and ribavirin.

In conclusion, twice-weekly dosing of peg-IFN-α-2a in combination with ribavirin resulted in superior early virologic response rates, superior viral kinetics, pharmacokinetics, pharmacodynamics, and superior ISG induction, although this study was not powered to analyze SVR. The results of this pilot study show promise for a more effective therapy, particularly for HIV/HCV genotype-1 co-infected African–Americans. Future studies are warranted to validate the clinical utility of using twice-weekly peg-IFN treatment to improve SVR among HCV and HIV co-infected patients.

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