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Peginterferon-α-2a (40kD) Plus Ribavirin

A Review of its Use in Hepatitis C Virus and HIV Co-infection

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Data Selection

Sources: Medical literature published in any language since 1980 on peginterferon alfa-2a plus ribavirin, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'peginterferon alfa-2a' and 'ribavirin' or 'pegylated interferon alfa-2a and ribavirin' and 'hepatitis C' and 'HIV infections'. EMBASE search terms were 'peginterferon alfa-2a' and 'ribavirin' and 'hepatitis C' and 'HIV' or 'human immunodeficiency virus'. AdisBase search terms were 'peg-interferon-alpha-2a' and 'ribavirin' or 'pegylated interferon alfa-2a' and 'ribavirin' and 'hepatitis-C' and 'HIV-infections'. Searches were last updated 9 November 2004.

Selection: Studies in patients with hepatitis C virus co-infected with HIV who received peginterferon alfa-2a and ribavirin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Peginterferon alfa-2a, ribavirin, hepatitis C infection, HIV, co-infection, pharmacodynamics, pharmacokinetics, drug interactions, tolerability, therapeutic use.

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Summary

Abstract

Pegylated interferon plus ribavirin is the standard first-line treatment in patients with chronic hepatitis C virus (HCV) mono-infection. Although the optimal anti-HCV regimen is not established in the more difficult-to-treat population with HIV-HCV co-infection, much of the data in this clinical setting have been derived from studies evaluating peginterferon-α-2a (40kD) [Pegasys®] plus ribavirin (Copegus®), most notably the APRICOT (AIDS Pegasys Ribavirin International Co-Infection Trial) and the ACTG (AIDS Clinical Trial Group) A5071 study. In particular, results of APRICOT – the largest study conducted to date with a pegylated interferon plus ribavirin in patients with HIV-HCV co-infection – indicate that a substantial proportion of patients will achieve sustained virological response (SVR) at week 72 when these drugs are administered for 48 weeks in an appropriate dosage regimen. In general, the tolerability profile of peginterferon-α-2a plus ribavirin in APRICOT was similar to that previously reported in patients with HCV mono-infection.

Pharmacological Properties

Interferons inhibit viral replication and/or function in infected cells via complex intracellular signalling processes induced by binding to specific cell surface receptors. The mechanism by which ribavirin exerts its antiviral effects against HCV is not known. Both peginterferon-α-2a and ribavirin have immunomodulatory effects, which may contribute to their activity.

Following subcutaneous administration of peginterferon-α-2a 180μg once weekly in patients with HCV infection, serum drug concentrations are sustained throughout the dosage interval, with peak concentrations approximately 1.5- to 2-fold higher than trough concentrations. Mean terminal elimination half-life ($t_{1/2}\beta$) of peginterferon-α-2a is 80 hours compared with 5.1 hours for interferon-α-2a.

Ribavirin is rapidly and extensively absorbed following oral administration, although absolute bioavailability is only about 45–65%, probably as a result of first-pass metabolism. The drug has a very high volume of distribution (4500L) and long $t_{1/2}\beta$ (120–170 hours). Pharmacokinetic properties of ribavirin are similar in patients with HIV-HCV co-infection or HCV mono-infection.

Concomitant administration of peginterferon-α-2a and ribavirin in patients with HCV infection did not result in any pharmacokinetic interaction between these drugs. There is also no clinically significant interaction between peginterferon-α-2a and methadone.

A pharmacokinetic analysis in almost 50 patients with HIV-HCV co-infection receiving anti-HCV and antiretroviral therapy showed that ribavirin 800 mg/day does not affect the intracellular metabolism or plasma concentration-time profile of lamivudine (3TC), stavudine (d4T) and zidovudine (AZT). However, didanosine (ddI) is not recommended (and is generally strictly avoided in clinical practice) in patients receiving ribavirin, as fatalities and other serious adverse effects associated with didanosine have occurred as a result of increased formation of its active triphosphate anabolite.

Therapeutic Efficacy

Optimal regimens of subcutaneous pegylated interferon plus oral ribavirin achieve SVR rates, defined as an undetectable HCV RNA level at the end of a 24-week untreated follow-up period, in excess of 50–60% in previously untreated patients with HCV mono-infection. However, SVR rates are typically much lower in patients with HIV-HCV co-infection.

SVR was achieved in 40% of co-infected patients who received peginterferon-α-2a 180μg once weekly plus ribavirin 800 mg/day as first-line therapy for 48 weeks in the large (n = 860), multinational study known as APRICOT. This was significantly higher than the SVR rate of 20% with peginterferon-α-2a monotherapy, or the 12% SVR rate with interferon-α-2a plus ribavirin. The difference in SVR rates between the latter two regimens was also statistically significant, indicating that peginterferon-α-2a monotherapy is a viable treatment option in co-infected patients who are unable to take ribavirin. The pattern of SVR (peginterferon-α-2a plus ribavirin > peginterferon-α-2a > interferon-α-2a plus ribavirin) remained the same when patients were grouped according to HCV genotype (1 vs 2 or 3) or by HCV RNA levels (high vs low) at baseline.

First-line therapy with peginterferon-α-2a 180μg once weekly plus ribavirin also achieved a significantly higher SVR rate than interferon-α-2a plus ribavirin (27% vs 12%) in 133 co-infected patients randomised in the ACTG A5071 study. A dose-escalation schedule for ribavirin was used in the ACTG A5071 study, which may not have provided optimal therapy.

Tolerability

In general, the tolerability profile of peginterferon-α-2a plus ribavirin appears to be similar in patients with HIV-HCV co-infection to that in patients with HCV mono-infection. In addition, combination therapy with peginterferon-α-2a plus ribavirin was not associated with loss of HIV disease control in co-infected patients.

In the APRICOT study in patients with HIV-HCV co-infection, the most frequently reported adverse events with peginterferon-α-2a plus ribavirin (incidence ≥20%) were fatigue, pyrexia, headache, myalgia, nausea, diarrhoea, insomnia, asthenia and depression. Premature withdrawal from the trial because of adverse events or laboratory abnormalities occurred in 15% of patients in this treatment group, and 8% experienced a serious treatment-related adverse event. In general, there were few differences between treatment groups for most of these tolerability parameters. Although statistical analysis was not reported, clinically significant neutropenia was more likely to occur in treatment arms that included

peginterferon-α-2a, and anaemia was more likely in treatment arms that included ribavirin.

In the ACTG A5071 trial, 12% of patients in both treatment groups discontinued therapy because of adverse events or laboratory abnormalities. The incidence of depression, influenza-like symptoms and laboratory abnormalities was also similar between treatment groups, although neutropenia of any grade was reported during the first 24 weeks of the trial in 55% of patients treated with peginterferon-α-2a plus ribavirin compared with 30% of those who received interferon-α-2a plus ribavirin (statistical analysis not reported).

1. Introduction

As many as one-third of HIV-infected individuals are thought to be co-infected with hepatitis C virus (HCV),[1,2] although the prevalence can vary widely and depends largely on the mode of HIV transmission.[1,3] Both HIV and HCV are RNA viruses and share common routes of transmission,[4,5] but HCV infection is primarily transmitted by percutaneous exposure, and the majority of individuals with chronic HCV infection have a history of intravenous drug use or received blood transfusions prior to the introduction of HCV blood-screening techniques.[6] For example, in a large French cohort of HIV-infected individuals, the prevalence of HCV co-infection was 91% among intravenous drug users and 71% in recipients of blood or blood products, but only 7% in those with sexually transmitted HIV.[7]

Cirrhosis develops in approximately 20–25% of patients with HCV infection[4,8] and can subsequently lead to complications such as ascites, encephalopathy, variceal bleeding and hepatocellular carcinoma.[4] The average duration of infection before the onset of cirrhosis is about 20 years in patients with HCV mono-infection,[9] although the range can be wide.[4] Historically, the impact of HCV infection on overall morbidity and mortality in co-infected patients was minimal because of the relatively poor prognosis among patients with HIV infection prior to the introduction of highly active antiretroviral therapy (HAART).[5] However, with the marked improvement in survival following the introduction of protease inhibitors and HAART,[10-12] co-infection with HCV has become a significant cause of morbidity and mortality in this population.[3,5,13]

For patients with chronic HCV mono-infection who are deemed to be suitable candidates for medical treatment, the current standard of care involves the use of pegylated interferon plus ribavirin.[4,14,15]

This recommendation stems from results of large, randomised, multicentre trials in patients with chronic HCV infection, which showed that sustained virological response (SVR) rates achieved with such regimens are superior to those achieved with alternative regimens, including conventional interferon plus ribavirin or pegylated interferon without ribavirin.[16-19] In pivotal trials, overall rates of SVR were up to 63% with optimal regimens of peginterferon-α-2a plus ribavirin[17-19] and 54% with peginterferon-α-2b plus ribavirin[16] as initial treatment of chronic HCV infection. Additional data indicate that peginterferon-α-2a plus ribavirin can also achieve SVR in selected patients with chronic HCV infection not responding to previous conventional interferon-based therapy, a difficult patient population to treat.[20]

The management of patients with HIV-HCV co-infection presents its own challenges, as this group of patients has a reduced response rate to anti-HCV therapy, a higher relapse rate following treatment, and accelerated progression to HCV-related liver disease compared with HCV mono-infected patients.[3,5,21,22] Some of the possible contributing factors are highlighted in table I. In addition, HCV co-infection may have an adverse effect on HIV disease progression, although data are less clear than for the

Table I. Factors potentially contributing to the reduced efficacy of anti-hepatitis C virus (HCV) therapy and accelerated liver disease in patients with HIV-HCV co-infection[3,5,21,22]

Reduced immunomodulatory activity of anti-HCV therapy in the setting of HIV-related immune dysfunction
Reduced spontaneous clearance of HCV after acute infection and, therefore, increased likelihood of chronic HCV viraemia
Low CD4+ cell count facilitates greater injury to hepatocytes
More advanced liver fibrosis grade at baseline, higher HCV RNA titres (in plasma and liver tissue), higher rate of steatosis
Greater incidence of hepatotoxicity from antiretroviral therapy
Higher rate of anti-HCV treatment discontinuation because of adverse events (or suboptimal management of adverse events)

influence of HIV disease on the outcome of chronic HCV infection.[3,5,21,22]

While there is currently no standard therapy for the management of chronic HCV infection in patients with HIV co-infection, proposed guidelines or recommendations focus on the use of pegylated interferons plus ribavirin (section 7).[15,21,23] As more data emerge, recommendations will be further refined for the optimal use of these drugs in patients with HIV-HCV co-infection. Much of the current and emerging data on the management of chronic HCV infection in HIV-infected patients involves the use of peginterferon-α-2a (40kD) [Pegasys®][1] plus ribavirin (Copegus®), which is the focus of this review. The use of peginterferon-α-2a plus ribavirin in the management of chronic HCV mono-infection has been previously reviewed in *Drugs*.[24]

2. Pharmacodynamic Properties

As might be expected, pharmacodynamic data on peginterferon-α-2a plus ribavirin specifically in patients with HIV-HCV co-infection are lacking. Therefore, this section provides a brief overview of the pharmacodynamic properties of these drugs (administered alone or in combination) in healthy volunteers and patients with HCV mono-infection. More detailed reviews on the pharmacodynamic properties of these drugs are also available.[24-26]

2.1 Antiviral Activity

Interferons bind to specific cell surface receptors of virus-infected cells, which induces a complex cascade of protein-protein interactions and rapid activation of gene transcription.[24,25,27] This intracellular signalling process results in the production and release of numerous effector proteins that can modulate various biological effects, including the inhibition of viral replication and/or function in infected cells. Pegylation of interferon-α-2a augments its antiviral activity, as shown by more sustained serum levels of the effector protein 2′, 5′-oligoadenylate synthetase with peginterferon-α-2a than with conventional interferon-α-2a in healthy volunteers.[28]

Subcutaneous administration of peginterferon-α-2a 180μg per week is associated with a biphasic decline in HCV RNA levels in patients with chronic hepatitis C.[29] The initial phase occurs within the first 48 hours of administration and probably results from inhibition of HCV replication and degradation of the free virus.[24,29] The second phase of HCV RNA decline, which is thought to reflect the degradation rate of infected cells, is characterised by a relatively stable exponential decay.[29]

Ribavirin is a synthetic nucleoside analogue and the mechanism by which it exerts its anti-HCV effects is not clearly established,[24,30] although data from a viral kinetics study suggest that ribavirin has weak and/or delayed antiviral activity against HCV.[31] Importantly, clinical trial data suggest that exposure to ribavirin, particularly early in the course of therapy,[20] is an important factor in preventing relapse and achieving SVR.[20,32,33]

2.2 Immunomodulatory Effects

Peginterferon-α-2a and ribavirin have both demonstrated immunomodulatory effects, which could potentially contribute to their activity.[24] In patients with chronic hepatitis C, 48 weeks of treatment with

1 The use of trade names is for product identification purposes only and does not imply endorsement.

peginterferon-α-2a 180μg per week, with or without ribavirin 800–1200 mg/day (n = 28), induced a sustained, vigorous, HCV-specific, CD4+ T-helper 1 response that was multispecific (i.e. characterised by response to core and nonstructural HCV antigens).[34] In general, HCV-specific, CD4+ T-helper 1 responses with these attributes were more likely to be associated with SVR than responses that were more narrowly focused, of lower magnitude and short-lived, such as those typically observed in the conventional interferon-α-2a treatment arm (n = 14) of the study. In addition, serum levels of interferon-γ were high and interleukin (IL)-4 and IL-10 were low in patients who achieved SVR.[34]

In vitro and *in vivo* data indicate that ribavirin may modulate the helper T-cell response towards a type 1 (i.e. antiviral) cytokine-mediated immune response.[35-37] Ribavirin also inhibited DNA, RNA and protein synthesis, apoptosis of CD45+ and CD14+ cells, and the production of interferon-γ (a pro-inflammatory cytokine associated with hepatic inflammatory activity) in stimulated peripheral blood mononuclear cells (PBMC) isolated from patients with HCV infection, suggesting additional mechanisms for its therapeutic activity.[38]

3. Pharmacokinetic Profile

The pharmacokinetic properties of subcutaneous peginterferon-α-2a and oral ribavirin have been evaluated primarily in healthy volunteers and patients with HCV mono-infection, and only limited pharmacokinetic data are available in patients with HIV-HCV co-infection.[39] An overview of the mean pharmacokinetic properties of these agents is provided in table II.

Pegylation refers to the addition of an inert polyethylene glycol (PEG) polymer, which protects the interferon molecule from proteolytic degradation, reduces its immunogenicity and prolongs its systemic exposure through reduced renal clearance.[26,40,41]

Table II. Overview of the mean pharmacokinetic properties of subcutaneous peginterferon-α-2a and oral ribavirin[24,27,30,39,42-44]

Parameter	Peginterferon-α-2a (HCV)[24,27,42,44]a	Ribavirin (HCV)[30,43]b	Ribavirin (HIV-HCV)[39]c
t_{max} (h)	72–96[d]	2	
C_{min} at steady state (ng/mL)	16 (range: 4–28)[e]	1662 (800 mg/d); 2112 (1200 mg/d)	1444 (800 mg/d)
C_{max} at steady state (ng/mL)	25.6[f]	2748 (1200 mg/d)	2771 (800 mg/d)
AUC (ng • h/mL)	3330[f] (AUC_{168})	25 361 (AUC_{12}) [1200 mg/d]	23 476 (AUC_{12}) [800 mg/d]
Absolute bioavailability (%)	84	45–65	
Time to steady state (wk)	5–8	4	
Vd (L)	6–14[g]	4500	
$t_{½β}$ (h)	80 (range: 50–140)[h]	120–170[i]	
CL (L/h)	0.094[h]	26[i]	

a Although not always explicitly stated, most data appear to be from patients with HCV infection who received peginterferon-α-2a 180μg once weekly with or without daily ribavirin. Peginterferon-α-2a concentrations were measured in serum.

b Data from patients with HCV infection who received ribavirin (in two divided doses with food, where specified) in combination with peginterferon-α-2a. Ribavirin concentrations were measured in plasma.

c Data from patients with HIV-HCV co-infection who received ribavirin (in two divided doses, presumably with food) in combination with peginterferon-α-2a. Ribavirin concentrations were measured in plasma.

d Single-dose administration of peginterferon-α-2a in healthy volunteers.

e At week 48, 168h after administration of the last dose (presumably 180μg).

f After the last dose of peginterferon-α-2a 180μg once weekly for 48wk.

g At steady state following intravenous administration.

h Unclear whether after single- or multiple-dose administration.

i After single-dose administration.

AUC = area under the serum or plasma concentration-time curve; **CL** = total clearance; $\mathbf{C_{max}}$ = maximum serum or plasma drug concentration; $\mathbf{C_{min}}$ = minimum serum or plasma drug concentration; **HCV** = hepatitis C virus; $\mathbf{t_{½β}}$ = terminal elimination half-life; $\mathbf{t_{max}}$ = time to C_{max}; **Vd** = volume of distribution.

3.1 Peginterferon-α-2a

3.1.1 Absorption and Distribution

Approximately 80% of the peak serum concentration (C_{max}) is achieved within 24 hours of administration of a single dose of peginterferon-α-2a 180μg,[42] although C_{max} is not achieved until 3 or 4 days after administration.[27,42] Both C_{max} and area under the serum concentration-time curve (AUC) measurements of peginterferon-α-2a increase in a dose-proportional manner.[27,42]

After 48 weeks of once-weekly administration of peginterferon-α-2a in patients with chronic hepatitis C, the ratio of C_{max} to trough serum concentration (C_{min}) was approximately 1.5–2, indicating that serum concentrations are sustained throughout the dosage interval.[27,42] C_{min} and AUC values at week 48 were approximately double those at week 1, indicating accumulation of the drug with repeated administration.[27,45]

The volume of distribution approximates that of blood and extracellular fluid (table II), although data from rats indicate that peginterferon-α-2a is also distributed to the liver, kidney and bone marrow.[42]

3.1.2 Metabolism and Elimination

The metabolic fate of peginterferon-α-2a is not fully characterised, although in rats the majority of radiolabelled drug was excreted via the kidney.[42] In patients with chronic hepatitis C, the mean terminal elimination half-life ($t_{1/2}\beta$) of peginterferon-α-2a was 80 hours compared with 5.1 hours for conventional interferon-α-2a.[27] The $t_{1/2}\beta$ appears to reflect the elimination phase of the drug as well as its sustained absorption following subcutaneous administration.[42]

3.1.3 Special Patient Populations

Patients with end-stage renal disease undergoing haemodialysis have a 25–45% reduction in systemic clearance of peginterferon-α-2a, and thus require dosage adjustments.[42] Clearance is also reduced by ≈25% in patients with creatinine clearance between 1.2 and 2.4 L/h (20 and 40 mL/min),[42] and caution is advised if peginterferon-α-2a is used in patients with compromised renal function.[27,42] Systemic exposure (AUC) is moderately increased in elderly individuals but dosage adjustments are not necessary.[42] Likewise, HCV-infected patients with or without mild cirrhosis (Child-Pugh Classification A) who received peginterferon-α-2a had similar systemic exposure and pharmacokinetic profiles.[42]

3.1.4 Potential Drug Interactions

No pharmacokinetic interaction between peginterferon-α-2a and ribavirin was observed in patients receiving the drugs concomitantly for chronic hepatitis C.[42] Peginterferon-α-2a had only a moderate and clinically insignificant effect on methadone pharmacokinetics, increasing mean methadone pharmacokinetic parameters by approximately 10–15% after 4 weeks of concomitant treatment in patients with chronic hepatitis C.[27,46] Methadone had no significant effect on the pharmacokinetics or antiviral activity of peginterferon-α-2a.

In healthy volunteers, peginterferon-α-2a 180μg per week for 4 weeks did not affect the pharmacokinetic profiles of various drugs metabolised by cytochrome P450 (CYP) 3A4, 2C9, 2C19 and 2D6 isoenzymes, but did increase the AUC of theophylline (a CYP1A2 substrate) by 25–34%.[42,47] Serum theophylline concentrations should be monitored closely in patients receiving theophylline and peginterferon-α-2a concomitantly.[42]

3.2 Ribavirin

3.2.1 Absorption and Distribution

Following oral administration, ribavirin is rapidly and extensively (≈90%) absorbed, although absolute bioavailability is reduced (table II), probably as a result of first-pass metabolism.[43] In single-dose pharmacokinetic studies with ribavirin 200–1200mg, a linear relationship was shown between dose and AUC. Multiple-dose AUC_{12} values are approximately 6-fold greater than single-dose values, reflecting extensive accumulation of the drug.[43]

Mean steady-state pharmacokinetic parameters of ribavirin were recently reported in patients with HIV-HCV co-infection.[39] Patients were a subgroup of those participating in the large randomised trial known as APRICOT (see section 4 for acronym

definition),[48] and results are reported in table II.[39] Pharmacokinetic values were similar to those reported previously in HCV mono-infected patients receiving combination therapy in clinical trials.

The AUC_{192} and C_{max} of ribavirin increased by 42% and 66%, respectively, when a single oral 600mg dose was administered with a high-fat meal.[30,43] It is recommended that ribavirin be taken with food in order to achieve optimal plasma concentrations.

The volume of distribution of ribavirin is very high (table II), which may reflect the mechanism of cellular uptake of the drug across membranes, primarily via an e_s-type equilibrative nucleoside transporter found on almost all cell types.[43] Ribavirin nucleotides are sequestered in erythrocytes to such an extent that ribavirin concentration in whole blood is about 60 times that in plasma. Ribavirin does not bind to plasma proteins.[43]

3.2.2 Metabolism and Elimination

Ribavirin is metabolised by reversible phosphorylation and via a degradative pathway that forms an intermediate triazole carboxamide and yields a triazole carboxylic acid metabolite.[43] Ribavirin and its triazole metabolites are excreted renally. After single-dose administration, the $t_{1/2}\beta$ of ribavirin is about 120–170 hours (table II).[30] The long $t_{1/2}\beta$ of ribavirin (≈300 hours) observed after discontinuation of the drug probably reflects its slow elimination from non-plasma compartments.[43]

3.2.3 Special Patient Populations

The pharmacokinetics of ribavirin have not been assessed in elderly patients, although a population pharmacokinetic analysis of ribavirin indicates that age is not an important factor.[43] Hepatic dysfunction does not affect the single-dose pharmacokinetics of ribavirin, as patients with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B or C) had similar kinetic profiles to those of normal controls.[43]

Systemic clearance of ribavirin is significantly decreased in patients with renal dysfunction, and the drug is either not recommended (US prescribing information)[30] or should only be used if absolutely necessary (UK prescribing information)[43] in patients with compromised renal function. Plasma ribavirin concentrations are essentially unchanged by haemodialysis.[30,43]

3.2.4 Potential Drug Interactions in Patients with Hepatitis C Virus (HCV) and HIV Co-infection

In vitro data indicate that ribavirin does not inhibit CYP enzymes but does inhibit phosphorylation of zidovudine and stavudine, thus potentially reducing their antiretroviral activity.[30] Since potential interactions with antiretroviral agents are particularly relevant in patients with HIV-HCV co-infection, a nested pharmacokinetic analysis[39] was incorporated into the design of the APRICOT study in co-infected patients[48] (see section 4.1).

The main objective of the pharmacokinetic analysis was to evaluate the effect of ribavirin on the intracellular phosphorylation of lamivudine, stavudine and zidovudine.[39] The primary analysis included 47 patients with HIV-HCV co-infection who received concomitant therapy with ribavirin plus two of these nucleoside reverse transcriptase inhibitors (NRTIs) for 8–12 weeks. The intracellular AUC_{12} ratios in PBMCs for the triphosphate anabolites of lamivudine, stavudine and zidovudine and their corresponding endogenous nucleotide triphosphates were similar at baseline and week 12. Ratios were also similar when data from patients randomised to placebo or ribavirin were compared. These results indicate that ribavirin 800 mg/day does not affect the intracellular metabolism of these NRTIs in patients with HIV-HCV co-infection. Evaluation of plasma drug concentrations at baseline and week 12 also showed that ribavirin does not modify the plasma concentration-time profile of lamivudine, stavudine or zidovudine in co-infected patients.[39]

Ribavirin increases the formation of the active triphosphate anabolite of didanosine *in vitro* and in animals, thus raising concerns that adverse reactions related to didanosine could be increased when ribavirin and didanosine are used concurrently.[43] US prescribing information states that concomitant administration of ribavirin and didanosine is not recommended, as there have been reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis and symptomatic hyperlactataemia/lac-

Table III. Differential features of APRICOT (AIDS Pegasys Ribavirin International Co-Infection Trial) and ACTG (AIDS Clinical Trial Group) A5071

Feature	APRICOT[48]	ACTG A5071[49]
No. of pts in efficacy analysis	860	133
Ribavirin dosage regimen[a]	800 mg/d	600 mg/d × 4wk, then 800 mg/d × 4wk, then 1000 mg/d for duration of treatment
Primary endpoint	SVR rate at wk 72[b]	Virological response at wk 24[c]
Treatment protocol for pts with no virological response at wk 24[d]	Decision to continue or discontinue HCV therapy left to pt and study physician	Liver biopsy performed and HCV treatment continued in pts with histological response[e]
Number and type of study centres	95 centres in 19 countries	21 centres in the US
Genotype 1 (% of pts)	≈61	≈77.5
African Americans (% of pts)	≈11	≈33
Mean age of pts (y)	≈40	≈44.5
High baseline HCV RNA levels (% of pts)	72[f]	≈82.5[f]
Bridging cirrhosis/fibrosis (% of pts)	≈16[g]	≈10[g]
Patients with normal ALT levels included?	No	Yes[h]

a Administered orally and used in combination with subcutaneous peginterferon-α-2a or interferon-α-2a for a planned treatment duration of 48wk.

b Defined as a serum HCV RNA level of <50 IU/mL at the end of the 24wk untreated follow-up period (wk 72).

c Defined as a serum HCV RNA level of <60 IU/mL at wk 24.

d Pts were followed-up until wk 72, regardless of treatment status.

e Defined as ≥2-point improvement in the total histological activity index.

f HCV RNA level >800 000 IU/mL[48] or >1 million IU/mL.[49]

g Defined as fibrosis stage 4–6[48] or 5 or 6.[49]

h Approximately one-third of pts had normal ALT levels.

ALT = alanine aminotransferase levels; **HCV** = hepatitis C virus; **pt(s)** = patient(s); **SVR** = sustained virological response.

tic acidosis in clinical trials.[30] In view of the serious nature of this interaction, the concomitant use of didanosine and ribavirin is generally strictly avoided in clinical practice.

4. Therapeutic Efficacy in HIV-HCV Co-infection

The clinical efficacy of subcutaneous peginterferon-α-2a plus oral ribavirin in patients with HIV-HCV co-infection has been evaluated in multicentre, randomised, open-label (or partly blinded) trials.[48-52] In particular, two pivotal studies are available as fully published papers,[48,49] the multinational trial known as APRICOT (AIDS Pegasys Ribavirin International Co-Infection Trial)[48] and the US ACTG (AIDS Clinical Trial Group) study A5071.[49] Although both trials were conducted in patients who were naive to anti-HCV therapy prior to study enrolment, there were differences in study population, ribavirin dosage regimen, primary endpoint and other factors, as summarised in table III. A brief discussion highlighting some of the more important differences between the APRICOT and ACTG A5071 trials and their possible impact on the outcomes is also provided in section 7.

The planned duration of therapy in both trials was 48 weeks, although specific treatment protocols varied between studies (see table III and sections 4.1 and 4.2).[48,49]

The primary endpoint of APRICOT was SVR, which was defined as an undetectable serum HCV RNA level at the end of the 24-week untreated follow-up phase (i.e. week 72).[48] In ACTG A5071, however, the primary endpoint was virological response (undetectable HCV RNA) at week 24 of therapy.[49] The limit of detection for HCV RNA was <50[48] or <60[49] IU/mL (assessed using Cobas Amplicor HCV Test, version 2.0, Roche Diagnostics). An intent-to-treat (ITT) analysis was undertaken in both studies.[48,49]

For inclusion in either study, patients had to be ≥18 years of age with detectable HCV RNA, abnor-

mal liver histology and stable HIV disease.[48,49] Patients with liver cirrhosis were not excluded from the trials, but patients with decompensated liver disease or other severe concomitant illness were excluded. In general, patients were well matched for baseline disease characteristics across treatment groups in individual trials.

Efficacy results of APRICOT[48] (including additional analyses[33,53-55]) and ACTG A5071[49] are presented in sections 4.1 and 4.2. In addition, results of two Spanish trials in anti-HCV treatment-naive patients with HIV-HCV co-infection,[50,51] and another study in HIV-HCV co-infected patients who had not responded to previous conventional interferon-based therapy,[52] are reported in section 4.3. All three of these trials are available only as abstracts/posters.

4.1 APRICOT

APRICOT is the largest study conducted to date with a pegylated interferon plus ribavirin in patients with HIV-HCV co-infection.[48] Of 868 patients randomised to one of three treatment groups for 48 weeks, 860 received at least one dose of the study drugs and comprise the ITT population. Thus, 289 patients received peginterferon-α-2a 180μg once weekly plus ribavirin 800 mg/day, 286 were treated with peginterferon-α-2a 180μg once weekly plus placebo, and 285 received conventional interferon-α-2a 3 million IU three times weekly plus ribavirin 800 mg/day.

SVR was achieved in 40% of patients treated with peginterferon-α-2a plus ribavirin, 20% of those who received peginterferon-α-2a monotherapy, and 12% of conventional interferon-α-2a plus ribavirin recipients (figure 1).[48] The difference in SVR rates between peginterferon-α-2a plus ribavirin and either comparator was statistically significant ($p < 0.001$), as was the difference in SVR rates between peginterferon-α-2a monotherapy and conventional interferon-based treatment ($p = 0.008$). The odds ratios for achieving SVR were as follows: 2.89 (97.5% CI 1.83, 4.58) for peginterferon-α-2a plus ribavirin versus peginterferon-α-2a monotherapy; 5.40 (97.5% CI 3.20, 9.12) for peginterferon-α-2a plus ribavirin versus conventional interferon-α-2a plus ribavirin; and 0.53 (97.5% CI 0.30, 0.91) for conventional interferon-α-2a plus ribavirin versus peginterferon-α-2a monotherapy.

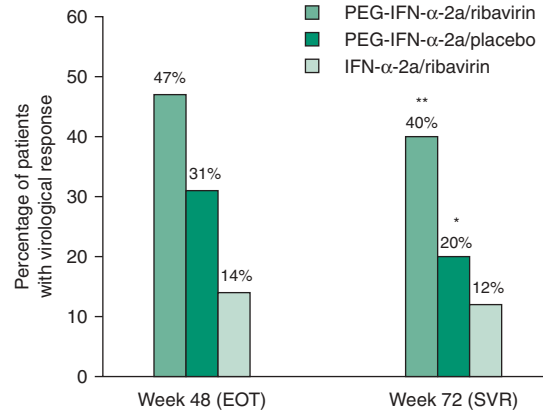

Fig. 1. Virological response rates in APRICOT (AIDS Pegasys Ribavirin International Co-Infection Trial).[48] Virological response rate at week 48 (end-of-treatment; EOT) and week 72 (sustained virological response; SVR) in patients with hepatitis C virus (HCV) and HIV co-infection who were randomised to receive one of three initial treatment regimens for chronic hepatitis C. Intent-to-treat analysis included 289 patients treated with subcutaneous peginterferon (PEG-IFN)-α-2a 180μg once weekly plus oral ribavirin 800 mg/day, 286 patients who received PEG-IFN-α-2a 180μg once weekly plus placebo, and 285 recipients of conventional interferon (IFN)-α-2a 3 million IU three times weekly plus ribavirin 800 mg/day. Statistical analysis not reported for EOT data. * $p = 0.008$ vs IFN-α-2a plus ribavirin; ** $p < 0.001$ vs either comparator.

Across the three treatment groups, 60–61% of patients were infected with HCV genotype 1 and 31–32% were infected with HCV genotypes 2 or 3.[48] As would be expected, SVR rates within each treatment group were numerically higher in patients with HCV genotypes 2 or 3 than in those with genotype 1 (figure 2). Across all three treatment groups, SVR rates by HCV genotype paralleled the overall SVR rates (figures 1 and 2). Statistical analysis was not reported for these comparisons, although an HCV genotype other than 1 was an independent factor associated with SVR (odds ratio 3.37; 95% CI 1.96, 5.80; $p < 0.001$).[48]

A similar pattern of response for the three treatment regimens was noted when grouped according to high and low baseline HCV RNA level; the best SVR rate was consistently achieved with peginterferon-α-2a plus ribavirin, followed by peg-

interferon-α-2a, then conventional interferon-α-2a plus ribavirin (statistical analysis not reported).[48] Among patients treated with peginterferon-α-2a plus ribavirin, SVR was achieved in 61% of those with a baseline HCV RNA level ≤800 000 IU/mL compared with 33% of those with a baseline HCV RNA level >800 000 IU/mL. Similarly, in the other treatment groups, SVR rates were markedly lower in patients with (than in those without) high baseline levels of HCV RNA. Thus, a baseline HCV RNA level of ≤800 000 IU/mL was also an independent factor associated with SVR in APRICOT (odds ratio 3.56; 95% CI 2.00, 6.36; $p < 0.001$).[48] However, when evaluated by HCV genotype, baseline HCV RNA level did not appear to have an effect on SVR rates in patients infected with HCV genotypes 2 or 3 (at least in patients receiving peginterferon-α-2a-based therapy).[48]

HIV factors, such as the CD4+ cell count at baseline and the use or nonuse of antiretroviral therapy, did not affect SVR rates.[48] These results suggest that anti-HCV therapy can be successful even in co-infected patients with more severe HIV disease, such as those with low CD4+ cell counts.

In APRICOT, the lack of an early virological response (defined as an undetectable HCV RNA level or a ≥2 $\log_{10}$ reduction in HCV RNA by week 12) was a strong negative predictor of SVR at week 72 (figure 3).[48] Across all three treatment groups, only 2 of 391 patients (0.5%) without an early virological response went on to achieve SVR, therefore the negative predictive value of achieving SVR was 99.5%. Both patients were in the peginterferon-α-2a plus ribavirin group, and the negative predictive value in this group was 98%. When using 24-week virological outcomes, the negative predictive value of achieving SVR was similar,[48] although the negative predictive value of 4-week virological outcomes was not as good (88% for peginterferon-α-2a plus ribavirin).[53] The predictive value of 12-week virological outcomes in APRICOT was similar to that in the ACTG A5071 study (figure 3 and section 4.2) and in patients with HCV mono-infection treated with peginterferon-α-2a plus ribavirin,[17] and these results may help to guide treatment decisions.[14] The positive predictive value of an early virological response in APRICOT was less robust than the negative predictive value.[48] Of the 204 patients who achieved an early virological response at week 12 with peginterferon-α-2a plus ribavirin, 114 (56%) had SVR at week 72.

In both treatment groups in which patients received concomitant ribavirin, approximately 75% of those who achieved a virological response at the end of therapy maintained virological response at the end of follow-up, according to a separate report of week 72 data from the APRICOT study.[33] Thus, virological response was maintained in 102 of 136 patients in the peginterferon-α-2a plus ribavirin group and 30 of 40 patients in the interferon-α-2a plus ribavirin group. This compares with 49 of 90 patients (54%) who maintained virological response in the peginterferon-α-2a monotherapy group. These data are derived from 834 patients for whom both end-of-treatment and end-of-follow-up data are

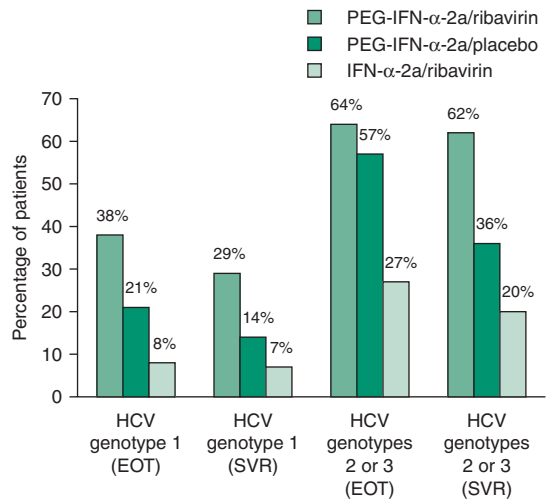

Fig. 2. Virological response rates according to hepatitis C virus (HCV) genotype in APRICOT (AIDS Pegasys Ribavirin International Co-Infection Trial).[48] Virological response rate at week 48 (end-of-treatment; EOT) and week 72 (sustained virological response; SVR) in patients with HIV-HCV co-infection who were randomised to receive one of three initial treatment regimens for chronic hepatitis C. Intent-to-treat analysis included 289 patients treated with subcutaneous peginterferon (PEG-IFN)-α-2a 180μg once weekly plus oral ribavirin 800 mg/day, 286 patients who received PEG-IFN-α-2a 180μg once weekly plus placebo, and 285 recipients of conventional interferon (IFN)-α-2a 3 million IU three times weekly plus ribavirin 800 mg/day. Statistical analysis not reported.

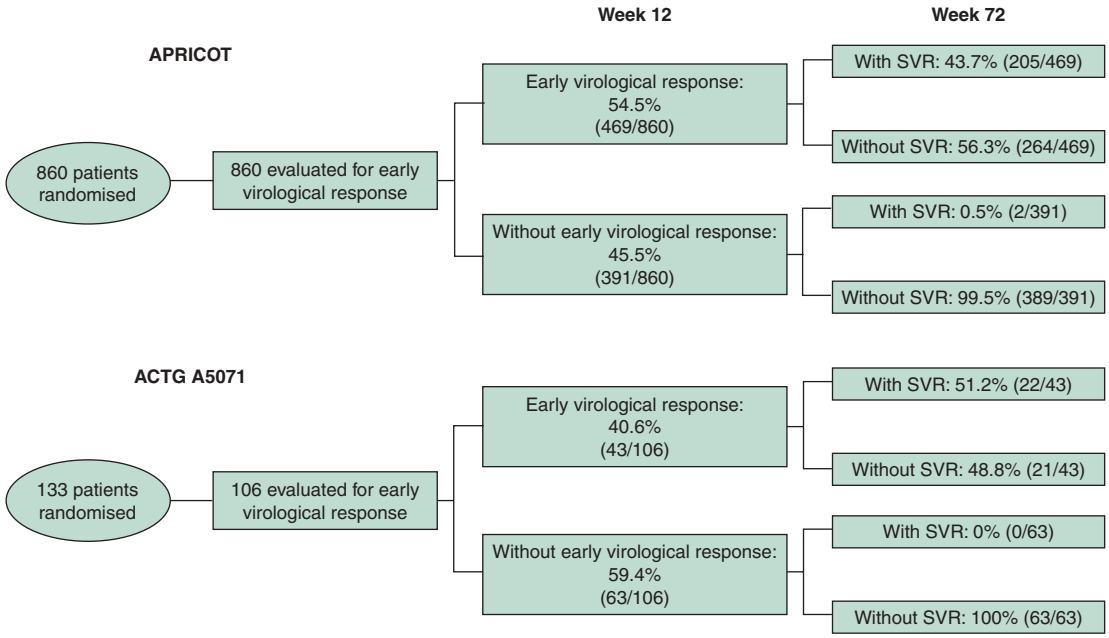

Fig. 3. Predictive value of early virological response in APRICOT (AIDS Pegasys Ribavirin International Co-Infection Trial)[48] and the ACTG (AIDS Clinical Trial Group) A5071 trial.[49] For each study, the figure shows the proportion of patients with hepatitis C virus (HCV) and HIV co-infection who had an early virological response to anti-HCV therapy at week 12 (undetectable HCV RNA levels or ≥2 $\log_{10}$ reduction from baseline) and achieved sustained virological response (SVR) at week 72 (i.e. positive predictive value), and the proportion of patients who did not have an early virological response and did not achieve SVR (i.e. negative predictive value). Data presented for each study are for treatment groups combined; randomised patients indicates intent-to-treat population who received at least one dose of study medication.

available (i.e. 26 patients had SVRs but did not have 48-week data and were therefore excluded from the analysis). Although statistical analysis was not reported, these results appear to indicate that the addition of ribavirin to interferon-based therapy prevents relapse in patients with HIV-HCV co-infection.[33]

In a separate analysis of APRICOT data,[55] peginterferon-α-2a plus ribavirin was associated with the highest rate of histological response (≥2-point reduction in the Ishak-modified histological activity index score), which was consistent with the overall virological outcome in APRICOT.[48] In the histological analysis, a representative sample of liver biopsies was obtained from patients who achieved SVR and those who did not.[55] Biopsy findings improved or were unchanged from baseline in most patients who achieved SVR. Histological improvement also occurred in a substantial proportion of patients who did not achieve SVR, suggesting that (as in HCV mono-infection) histological response could be an alternative goal of therapy in patients with HIV-HCV co-infection.[55]

In a subanalysis of APRICOT in patients treated with peginterferon-α-2a plus ribavirin, health-related quality of life (HR-QOL) was shown to be better in those who achieved SVR than in those who did not.[54] HR-QOL was evaluated at various time points using two instruments with good validity in patients with chronic hepatitis C, the Short Form (SF)-36 Health Survey and the Fatigue Severity Scale (FSS). The SF-36 is a generic instrument with 36 items and eight domain scales; domain scale scores are linearly transformed into a scale from 0 (worst health) to 100 (best health). The ten-item FSS includes a survey of nine items, which are combined into a total fatigue score, as well as a 100mm visual analogue scale (VAS) of fatigue severity; higher FSS scores indicate worsening fatigue. Results showed that HR-QOL scores were numerically better on seven of the eight SF-36 domains and both

the total fatigue and fatigue severity scores of the FSS. Statistically ($p < 0.05$) and clinically (>3 points) significant differences favouring patients who achieved SVR were reported for the vitality and general health domains of the SF-36 as well as the FSS VAS score.[54]

4.2 ACTG A5071

In the ACTG A5071 trial, 133 patients with HIV-HCV co-infection were randomised to receive 48 weeks of treatment with ribavirin plus either peginterferon-α-2a 180μg once weekly or interferon-α-2a 6 million IU three times weekly for 12 weeks, followed by 3 million IU three times weekly for 36 weeks.[49] In an effort to reduce the risk of treatment-limiting anaemia in this high-risk population, ribavirin was administered according to a dose-escalation schedule. The initial ribavirin dosage was 600 mg/day, which was increased to 800 mg/day after 4 weeks, then to 1000 mg/day from week 8 onwards if tolerated.

Virological response at week 24 was the primary endpoint of ACTG A5071, and this was achieved in 44% of patients treated with peginterferon-α-2a plus ribavirin compared with 15% of those who received interferon-α-2a plus ribavirin ($p < 0.001$).[49] Similar results were reported for virological response at the end of treatment (week 48) [figure 4].

Peginterferon-α-2a plus ribavirin achieved a significantly higher SVR rate than interferon-α-2a plus ribavirin (27% vs 12%; $p = 0.03$) [figure 4].[49] When patients were grouped according to HCV genotype, peginterferon-α-2a plus ribavirin achieved SVR in 14% of those with genotype 1 compared with 73% with genotype non-1 ($p < 0.001$); corresponding results for patients treated with interferon-α-2a plus ribavirin were 6% and 33% ($p < 0.001$).

As was the case in the APRICOT study (section 4.1), a lack of virological response at week 12 was a strong negative predictor of SVR in the ACTG A5071 trial (figure 3).[49] None of the 63 patients who did not have a reduction in HCV RNA levels by ≥2 $\log_{10}$ IU/mL or to undetectable levels at week 12 achieved SVR at week 72. Approximately half of the 43 patients who had an early virological response achieved SVR.

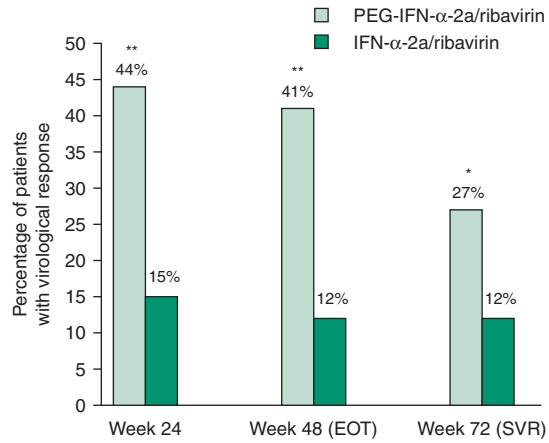

Fig. 4. Virological response rates in the ACTG (AIDS Clinical Trial Group) A5071 study.[49] Virological response rates at week 24 (primary endpoint), 48 (end of treatment; EOT) and 72 (sustained virological response; SVR) among 133 patients with hepatitis C virus (HCV) and HIV co-infection who were randomised to receive subcutaneous peginterferon (PEG-IFN)-α-2a 180μg once weekly plus ribavirin or interferon (IFN)-α-2a 6 million IU three times weekly for 12 weeks followed by 3 million IU three times weekly for 36 weeks plus ribavirin. Ribavirin was administered orally in a dose-escalation schedule, starting at 600 mg/day and gradually increased up to 1000 mg/day if tolerated. Analysis was for the intent-to-treat population. * $p = 0.03$, ** $p < 0.001$ vs comparator.

As mentioned earlier in table III, patients in the ACTG A5071 trial who did not achieve virological response at week 24 underwent liver biopsy to evaluate histological response. Among patients for whom this occurred, approximately 35% of patients in both treatment groups met the criteria for histological response, and treatment was continued.[49]

4.3 Other Studies

Preliminary results from two Spanish trials with peginterferon-α-2a-based therapy in patients with HIV-HCV co-infection are also available.[50,51] In the larger study, 311 patients received 4 weeks of treatment with peginterferon-α-2a 180μg per week, at which time virological response was evaluated.[50] Patients with undetectable HCV RNA levels continued peginterferon-α-2a monotherapy until week 48, while patients who did not achieve a virological response at week 4 received combination therapy

with the addition of ribavirin 800 mg/day. SVR rates of 64% and 33% were achieved in patients with and without an early virological response (data from 105 patients). These results suggest that peginterferon-α-2a monotherapy may be a viable treatment option for patients who are unable to tolerate concomitant ribavirin.[50]

The other Spanish trial is evaluating peginterferon-α-2a 180μg per week in combination with two different dosage regimens of ribavirin (800 or 1000 mg/day).[51] Interim results from 97 patients showed virological response rates at the end of treatment (week 48) were 29% and 43% for those receiving the lower and higher dosages of ribavirin as concomitant therapy (statistical analysis not reported).

In a third trial, almost 20% of patients (8 of 41) with HIV-HCV co-infection who had not responded to ≥12 weeks of previous interferon-based therapy achieved SVR with peginterferon-α-2a plus ribavirin compared with approximately 6% (2 of 35) of those who received peginterferon-α-2a monotherapy (not statistically significant; ITT analysis).[52] Patients enrolled in the study were randomised to receive peginterferon-α-2a 180μg per week with or without ribavirin 800 mg/day. For patients randomised to peginterferon-α-2a monotherapy, ribavirin was added to therapy at week 24 if the reduction from baseline in HCV RNA levels was at least 2 $\log_{10}$. Study treatment was discontinued if there was not a virological response at week 24.

5. Tolerability

5.1 APRICOT

Tolerability data from the large, randomised APRICOT study (section 4.1)[48] are presented in table IV and figure 5. In each of the three treatment groups, at least one adverse event was reported in 95–96% of patients. The most frequent adverse events (reported in 20–44% of patients) were fa-

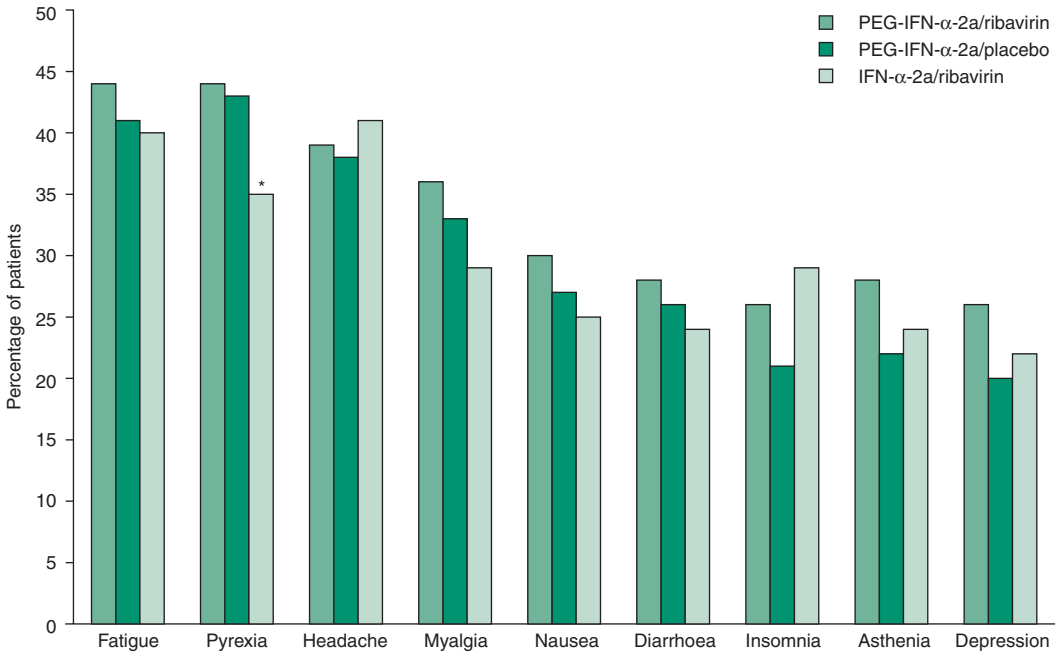

Fig. 5. Most frequently reported adverse events in APRICOT (AIDS Pegasys Ribavirin International Co-Infection Trial), a multinational trial in patients with HIV-hepatitis C virus co-infection.[48] Patients were randomised to 48 weeks of therapy with subcutaneous peginterferon-α-2a (PEG-IFN-α-2a) 180μg once weekly plus oral ribavirin 800 mg/day, PEG-IFN-α-2a 180μg once weekly plus placebo, or conventional interferon-α-2a (IFN-α-2a) 3 million IU three times/wk plus ribavirin 800 mg/day. * p = 0.03 vs PEG-IFN-α-2a plus ribavirin.

Table IV. Tolerability data from APRICOT (AIDS Pegasys Ribavirin International Co-Infection Trial), a multinational trial in patients (pts) with HIV-hepatitis C virus co-infection.[48] Pts were randomised to receive subcutaneous peginterferon-α-2a (PEG-IFN-α2a) 180μg once weekly plus oral ribavirin 800 mg/d, PEG-IFN-α-2a 180μg once weekly plus placebo, or conventional interferon-α-2a (IFN-α2a) 3 million IU three times weekly plus ribavirin 800 mg/d for 48wk

Parameter	PEG-IFN-α-2a + ribavirin (n = 289)	PEG-IFN-α-2a + placebo (n = 286)	IFN-α-2a + ribavirin (n = 285)
Discontinuation due to adverse event or laboratory abnormality (%)	15	16	15
Serious adverse event (treatment-related[a]) [%]	8	10	5
Death (from any cause) [no. of pts]	4	5	3
Death (treatment-related[a]) [no. of pts]	1	0	1
Hepatic decompensation (no. of pts)	5	5	4
Grade 4 neutropenia[b] (%)	11	13	<1

a Considered possibly or probably treatment related.

b Neutrophil count <500 cells/mm3.

tigue, pyrexia, headache, myalgia, nausea, diarrhoea, insomnia, asthenia and depression. The incidence of each of these adverse events was similar across all three treatment groups, with the exception of pyrexia, which was reported in significantly fewer patients who received conventional interferon-α-2a plus ribavirin than those who were treated with peginterferon-α-2a plus ribavirin (figure 5).[48]

Among the 289 patients treated with peginterferon-α-2a plus ribavirin, 15% discontinued therapy because of adverse events or laboratory abnormalities, and 8% experienced a serious treatment-related adverse event (table IV).[48] Although statistical analysis was not reported, these frequencies were similar to those reported for patients treated with conventional interferon-α-2a plus ribavirin or peginterferon-α-2a plus placebo. Serious treatment-related adverse events included lower respiratory tract infections, anaemia, thrombocytopenia, drug abuse, and a range of other problems. Treatment-related deaths were rare across the three groups (table IV). Hepatic decompensation occurred in a total of 14 patients and was evenly distributed across treatment groups (table IV; additional details reported in section 5.1.1). Pancreatitis, symptomatic hyperlactataemia and lactic acidosis each occurred in ≤1% of patients in each treatment group. Grade 4 neutropenia was reported in numerically more patients treated with peginterferon-α-2a-based therapy than interferon-α-2a-based therapy (table IV).

Neutropenia and anaemia are the most common laboratory abnormalities necessitating dosage modifications of peginterferon-α-2a and ribavirin, respectively.[56] In the APRICOT trial,[48] 27% of patients in both peginterferon-α-2a treatment arms had neutropenia requiring dosage modification of the drug. In comparison, 3% of patients in the interferon-α-2a treatment arm developed neutropenia requiring dosage modification. In the ribavirin treatment arms, 11% and 16% of patients developed ribavirin-associated anaemia requiring dosage reduction. This compares with 6% of patients who had their placebo 'dosage' adjusted because of anaemia thought to be associated with the oral therapy. There was no statistical analysis for these comparisons.

In a separate analysis,[57] tolerability data for peginterferon-α-2a 180μg once weekly plus ribavirin 800 mg/day in patients with HIV-HCV co-infection in the APRICOT study[48] were compared with those from a multinational trial[18] in patients with HCV mono-infection who were treated with the same regimen. In general, the tolerability profile of peginterferon-α-2a plus ribavirin was similar in both patient populations.[57] There were no statistically significant differences in the incidence of treatment-related serious adverse events, discontinuation of study treatment because of adverse events or laboratory abnormalities, or ribavirin dosage reductions because of adverse events or laboratory abnormalities, although the incidence was numerically higher in patients with HIV-HCV co-infection than

in those with HCV mono-infection for some of these parameters.[57]

5.1.1 Hepatic Decompensation

A substudy of APRICOT (section 4.1) examined the risk factors associated with hepatic decompensation in HIV-HCV co-infected patients treated with anti-HCV therapy.[58] Among the 868 patients enrolled in the trial, 133 (15.3%) had liver cirrhosis, and hepatic decompensation was observed in 14 of these 133 patients (10.5%) during anti-HCV therapy; the vast majority of cases (13 of 14) occurred during the first 24 weeks. Of the 14 patients with hepatic decompensation, five were treated with peginterferon-α-2a plus ribavirin, five received peginterferon-α-2a monotherapy and four were recipients of interferon-α-2a plus ribavirin (table IV). Univariate and multiple logistic regression analysis showed that most risk factors for hepatic decompensation are biological markers for advanced cirrhosis (higher total bilirubin and alkaline phosphatase levels; lower albumin levels, haemoglobin and platelet count), highlighting the need for monitoring during therapy. Concomitant didanosine therapy was also a risk factor. Overall, results indicate that patients with mild cirrhosis may not be at increased risk of hepatic decompensation and should be considered for anti-HCV treatment.[58]

5.2 ACTG A5071

In the ACTG A5071 trial (section 4.2), 12% of patients in both treatment arms discontinued therapy because of adverse events or laboratory abnormalities.[49] The incidence of depression, influenza-like symptoms and laboratory abnormalities was also similar in patients randomised to receive 48 weeks of treatment with peginterferon-α-2a plus ribavirin or interferon-α-2a plus ribavirin.[49] During the first 24 weeks of therapy with these respective treatment regimens, influenza-like symptoms were reported in 47% and 49% of patients and depression occurred in 11% and 12% of patients; in all cases the severity was grade 2 or 3. During the first 24-week period, neutropenia of any grade occurred in 55% of patients randomised to peginterferon-α-2a plus ribavirin compared with 30% of those treated with interferon-α-2a plus ribavirin; severe (grade 4) neutropenia occurred in five and three patients, respectively. Grade 4 anaemia occurred in two patients treated with peginterferon-α-2a plus ribavirin and in no interferon-α-2a plus ribavirin recipients. Statistical analysis was not reported for any of these comparisons.[49]

5.3 Effect on HIV Disease

Combination therapy with peginterferon-α-2a and ribavirin was not associated with loss of HIV disease control in co-infected patients in clinical trials.[39,49,52] AIDS-defining events occurred in a total of ten patients during the 48-week treatment period or 24-week follow-up period in APRICOT.[48] These were distributed evenly among the three treatment groups (four events in the peginterferon-α-2a plus ribavirin group and three events in each of the other two groups). There were no AIDS-defining illnesses in the ACTG A5071 trial.[49]

In APRICOT, mean CD4+ cell counts decreased to a similar extent (by 131–157 cells/mm^3) across all three treatment groups, but the mean percentage of CD4+ lymphocytes increased slightly.[48] Similar results were reported for median CD4+ cell counts and CD4+ percentage in the ACTG A5071 trial.[49]

In the 40% of patients with detectable HIV RNA levels at baseline in APRICOT, a reduction in mean HIV RNA levels by about 0.7–0.8 $\log_{10}$ copies/mL was noted in treatment arms that included peginterferon-α-2a.[48] In the ACTG A5071 trial, 14% of patients treated with peginterferon-α-2a plus ribavirin and 11% of those who received interferon-α-2a plus ribavirin had detectable HIV RNA levels at baseline that became undetectable at week 24.[49] Conversely, 5% and 6% of patients in the respective treatment groups had undetectable HIV RNA levels at baseline that became detectable at week 24.

6. Dosage and Administration

To date, prescribing information for peginterferon-α-2a and ribavirin do not provide official dosage recommendations for the management of chronic hepatitis C in patients with HIV co-infec-

tion.[27,30,42,43] In HCV mono-infection, the recommended regimen is peginterferon-α-2a 180μg subcutaneously once weekly plus ribavirin administered orally in two divided daily doses. For patients infected with HCV genotypes 1 or 4, ribavirin 1000 or 1200 mg/day (depending on whether bodyweight is <75kg or ≥75kg) is administered for 48 weeks; for patients infected with HCV genotypes 2 or 3, the recommended dosage is 800 mg/day for 24 weeks. However, as outlined below, currently available data indicate that treatment should be continued for 48 weeks in HIV-HCV co-infected patients, regardless of genotype, and there are concerns about increased toxicity in this patient population with ribavirin dosages above 800 mg/day.[15]

Practice guidelines from the American Association for the Study of Liver Diseases (AASLD), which were issued prior to publication of APRICOT or ACTG A5071, indicate that peginterferon plus ribavirin is the optimal therapy for most HIV-HCV co-infected patients, but stop short of providing definitive recommendations regarding optimal dosages and duration of therapy because of insufficient data.[15] In general, the AASLD suggests that dosage regimens derived from trials of HCV mono-infected patients are recommended for patients with HIV-HCV co-infection. However, abbreviated (24-week) courses of therapy for patients infected with HCV genotypes 2 or 3 have not been adequately evaluated in co-infected patients, and 48-week regimens have been evaluated in most clinical trials in this patient population.[15] Thus, until clinical trial data indicate otherwise, 48-week treatment regimens of peginterferon plus ribavirin should be used for all patients with HIV-HCV co-infection, regardless of HCV genotype.[15] The most effective treatment arm of the large, multinational APRICOT study in patients with HIV-HCV co-infection was subcutaneous peginterferon-α-2a 180μg once weekly plus oral ribavirin 800 mg/day for 48 weeks (section 4.1).[48] Ribavirin dosages above 800 mg/day, which are recommended for patients with HCV mono-infection (genotypes 1 or 4),[27] may lead to increased toxicity in patients with HIV-HCV co-infection.[15]

In both APRICOT[48] and ACTG A5071,[49] patients who did not achieve an early virological response after 12 weeks of therapy were highly unlikely to achieve SVR at week 72 (figure 3). Thus, as in patients with HCV mono-infection,[27] consideration should be given to discontinuing therapy in HIV-HCV co-infected patients without an early virological response at week 12.[48,49] In the ACTG A5071 study, about 35% of patients with no virological response at week 24 showed signs of histological improvement on liver biopsy (section 4.2), and it has been suggested that these findings should be considered when making decisions regarding early treatment discontinuation in patients with more advanced disease.[49]

Peginterferon-α-2a should be administered subcutaneously in the abdomen or thigh, as bioavailability is greater than when administered at other sites such as the arm.[27,42] Ribavirin is administered orally with food in two divided daily doses.[30,43]

Ribavirin has significant teratogenic effects and is contraindicated in pregnant women and their male partners.[27,30] Prescribing information for peginterferon-α-2a and ribavirin should be consulted for additional warnings, contraindications and precautions.[27,30,42,43]

7. Place of Peginterferon-α-2a Plus Ribavirin in the Management of HIV-HCV Co-infection

The treatment of chronic HCV infection in patients co-infected with HIV presents a difficult clinical challenge. Response to anti-HCV therapy is reduced and progression to HCV-related liver disease is accelerated in this difficult-to-treat population relative to patients with HCV mono-infection (section 1). Proposed guidelines or recommendations for the management of chronic HCV infection in patients with HIV co-infection advocate the use of pegylated interferons plus ribavirin,[15,21,23] and recent data from clinical trials such as APRICOT[48] and the ACTG A5071 trial[49] will help to further refine the optimal use of these drugs in patients with HIV-HCV co-infection. Both APRICOT and ACTG

A5071 were conducted in patients who had not previously received anti-HCV therapy.

In the large, multinational APRICOT study, peginterferon-α-2a 180μg once weekly plus ribavirin 800 mg/day for 48 weeks achieved a 40% SVR rate, which was superior to peginterferon-α-2a monotherapy (20%) or conventional interferon-α-2a plus ribavirin (12%) [section 4.1].[48] In general, the tolerability profile of peginterferon-α-2a plus ribavirin in this trial was similar to that observed previously in patients with HCV mono-infection (section 5). Importantly, the pattern of SVR observed for the three treatment groups in APRICOT (peginterferon-α-2a plus ribavirin > peginterferon-α-2a > interferon-α-2a plus ribavirin) was also consistent when patients were grouped according to HCV genotype (1 vs 2 or 3) or by HCV RNA levels at baseline (high vs low) [section 4.1].

In APRICOT, peginterferon-α-2a monotherapy achieved a SVR rate that was significantly higher than that achieved with interferon-α-2a plus ribavirin (20% vs 12%).[48] These results indicate that, in patients with HIV-HCV co-infection who are unable to take ribavirin, peginterferon-α-2a monotherapy is a viable treatment option. Another important finding from the trial is that the addition of ribavirin to either interferon-α-2a or peginterferon-α-2a was associated with a higher proportion of patients who maintained virological response from the end of treatment (week 48) to follow-up (week 72), thus suggesting that the addition of ribavirin to interferon-based therapy reduces the rate of relapse in HIV-HCV co-infected patients.[33]

In general, results of the APRICOT study are supported by those of the smaller, multicentre ACTG A5071 study conducted in the US, although there were some important differences between these trials in terms of dosage regimens, primary outcomes and patient populations (see table III). In the ACTG A5071 trial, peginterferon-α-2a plus ribavirin for 48 weeks achieved a significantly higher SVR than interferon-α-2a plus ribavirin (27% vs 12%) [section 4.2].[49] In both trials, patients who did not achieve an early virological response at week 12 had little or no chance of achieving SVR even if therapy was continued for 48 weeks.[48,49]

While the rate of SVR among patients treated with peginterferon-α-2a plus ribavirin was somewhat lower in ACTG A5071 than that reported in APRICOT, one possible explanation for the difference could be the ribavirin dose-escalation schedule used in ACTG A5071 (section 4.2), which may have provided suboptimal exposure to ribavirin, especially early in the course of therapy.[20] As mentioned in section 2.1, exposure to ribavirin appears to be an important factor in preventing relapse and achieving SVR.[20,32,33] The studies also used different primary endpoints: SVR was the primary endpoint of APRICOT, whereas ACTG A5071 used virological response at week 24 and was not adequately powered to evaluate SVR rates. In addition, there was a greater proportion of Black patients and patients infected with HCV genotype 1, as well as higher mean baseline HCV RNA levels and patient age in the ACTG A5071 trial than in the APRICOT study (table III).[48,49] These factors are associated with significantly lower SVR rates in patients with HCV mono-infection.[15,59] On the other hand, the incidence of bridging cirrhosis/fibrosis, which is also associated with reduced SVR rates in HCV mono-infection,[15,59] was numerically lower in the ACTG A5071 trial than in APRICOT (table III).

The optimal dosage regimen of ribavirin in patients with HIV-HCV co-infection is not known. Treatment guidelines for patients with HCV mono-infection recommend, in addition to pegylated interferon, a 24-week course of ribavirin 800 mg/day for patients infected with HCV genotypes 2 or 3, and a 48-week course of ribavirin 1000 or 1200 mg/day (depending on bodyweight) for those infected with HCV genotypes 1 or 4 (section 6).[14,15] However, ribavirin courses <48 weeks in duration have not been adequately studied in patients with HIV-HCV infection.[15] Indeed, limited data using a 24-week regimen of peginterferon plus ribavirin in co-infected patients with HCV genotypes 2 or 3 indicates a high relapse rate.[60] Therefore, the planned duration of anti-HCV therapy for patients with HIV-HCV co-infection should be 48 weeks, regardless of HCV

genotype.[15] There is also concern about ribavirin-associated anaemia with dosages higher than 800 mg/day in this patient population.[15]

Important data have also come from a nested pharmacokinetic analysis[39] in APRICOT,[48] which showed that ribavirin does not affect the intracellular metabolism or plasma concentration-time profile of commonly used NRTIs in patients with HIV-HCV co-infection (section 3.2.4).[39] However, didanosine appears to increase the risk of hepatic decompensation in patients with HIV-HCV co-infection and cirrhosis who are receiving anti-HCV therapy (section 5.1.1)[58] and is not recommended in patients receiving ribavirin because of an increased risk of adverse effects associated with didanosine (section 3.2.4).[30] Indeed, in view of the serious nature of this interaction (section 3.2.4), the concomitant use of didanosine and ribavirin is generally strictly avoided in clinical practice.

Data are also available on the use of peginterferon-α-2b (12kD) plus ribavirin as initial anti-HCV treatment for patients with HIV-HCV co-infection. Both peginterferon-α-2a and peginterferon-α-2b are approved for once-weekly administration in the treatment of chronic HCV infection, despite differences in pharmacokinetic properties.[44] Most clinical studies with peginterferon-α-2b plus ribavirin in patients with HIV-HCV co-infection have been small, noncomparative and/or single-centre trials,[60-63] other than the large (n = 412), multicentre RIBAVIC study.[64] In a single-centre trial involving 95 co-infected patients, SVR was achieved in 44% of those randomised to peginterferon-α-2b 100–150μg once weekly plus ribavirin 800–1200 mg/day compared with 21% who received interferon-α-2b 3 million IU three times weekly plus ribavirin ($p = 0.017$) for 48 weeks (or 24 weeks if genotypes 2 or 3 with HCV RNA <800 000 IU/mL at baseline).[63] In RIBAVIC, which had the same primary endpoint as APRICOT, SVR was achieved in 27% of patients who were randomised to receive 48 weeks of treatment with peginterferon-α-2b 1.5 μg/kg/week plus ribavirin 800 mg/day compared with 20% of those who received interferon-α-2b 3 million IU three times weekly plus ribavirin 800 mg/day ($p = 0.047$).[64] Primary efficacy results with peginterferon-α-2a plus ribavirin in the APRICOT study (SVR 40%) appear to be more favourable than in RIBAVIC, although comparisons between studies are not statistically valid and a randomised trial comparing these regimens is needed to draw any conclusions regarding their relative efficacy.

In conclusion, much of the current and emerging data on the management of chronic HCV infection in patients with HIV co-infection involves the use of peginterferon-α-2a plus ribavirin as initial therapy. In particular, results of the APRICOT study indicate that a substantial proportion of patients with HIV-HCV co-infection will achieve SVR when these drugs are administered in an appropriate dosage regimen.

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