

Pegylated Interferons: Clinical Applications in the Management of Hepatitis C Infection

S. James Matthews and Christopher McCoy

Introduction

Currently, there are two pegylated interferon (PEG-IFN) products available for the treatment of hepatitis C virus (HCV) infection [(pegylated interferon, PEG-IFN alpha-2a (PEGASYS[®]), and pegylated interferon, PEG-IFN alpha-2b (PEG-INTRON[®])]. Pegylation is a process by which the interferon-alpha is bound to a polyethylene glycol moiety (Kozlowski & Harris, 2001). The PEG-IFN-alpha-2a product is bound to a single-branched bis-monomethoxy polyethylene glycol (PEG) chain (40,000 daltons) for a final molecular weight of 60,000 daltons or 60 kDa (kilodaltons). Four major positional isomers exist for this compound (Bailon et al., 2001) In contrast, PEG-IFN-alpha-2b is formed by attaching a single chain of PEG (12 kDa mono-methoxy PEG) to interferon-alpha-2b via an ester linkage. The PEG moiety is conjugated to the His³⁴ amino acid residue, forming 12 positional isomers (Wang et al., 2000). The combined molecular weight of PEG-IFN-alpha-2b is smaller, about 31 kDa. The chemical structure and linkages of PEG-IFNs (alpha-2a and alpha-2b) are shown in Figure 1.

Pegylation does change the pharmacokinetic properties of unmodified interferon-alpha demonstrably (Luxon et al., 2002; Kozlowski & Harris, 2001). These properties allow for once-weekly dosing, more stable interferon-alpha blood concentrations throughout the dosing interval, and improved efficacy (Luxon et al., 2002; Pockros et al., 2004; Lindsay et al., 2001).

Currently, the National Institutes of Health identifies the use of PEG-IFN-alpha plus ribavirin (RBV) as the preferred therapy for the treatment of chronic HCV infection. While an improvement over rates of treatment success with unmodified interferons, the critical endpoint, a sustained virological response (SVR), defined as an undetectable level of HCV RNA 6 months after the completion of therapy, remains low particularly for genotype 1, at 42–52%. Higher rates are observed in patients with genotype 2 or 3, at 76–84% (Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001; National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C, 2002). Efforts to develop more effective dosing regimens, especially for subjects with genotype 1 and patients who do not respond or relapse after completion of therapy, are under study. This chapter will review the pharmacokinetics, efficacy in phase II and III clinical studies,

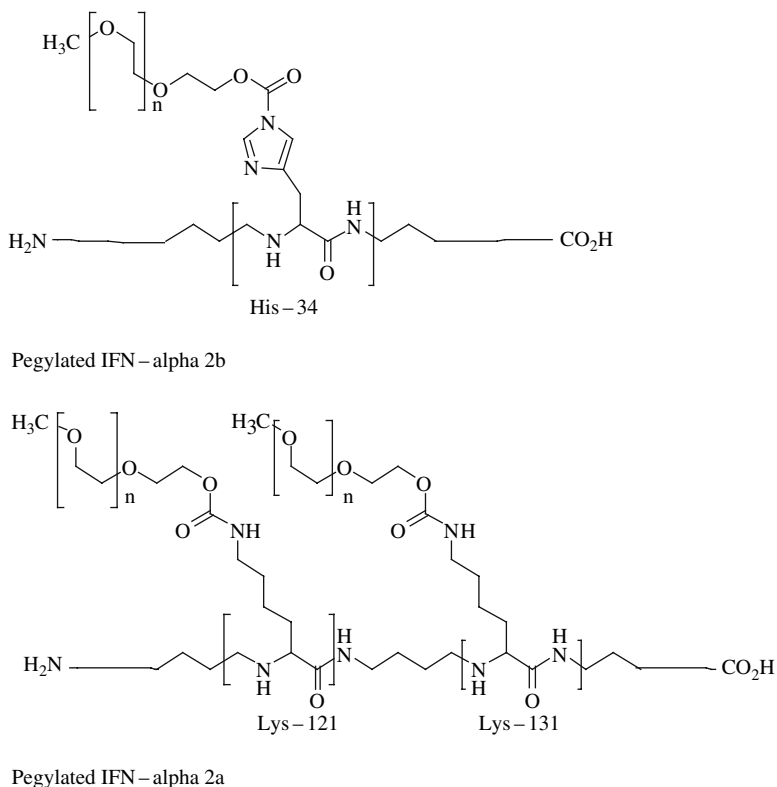


Fig. 1 Pegylated IFN-alpha 2a-Primary sites of pegylation are on amino terminus of the side chains of lysines-121 and 131

Pegylated IFN-alpha 2b-Primary site of pegylation is on imidazole side chain of histidine-34

and therapeutic options for the use of the PEG-IFNs in difficult-to-treat conditions. Safety and drug interaction considerations will also be reviewed.

Pharmacokinetics

This review will involve comparisons among unmodified interferon-alpha, PEG-INF-alpha-2a, and PEG-INF-alpha-2b. The pharmacokinetic parameters of the two PEG-IFNs are quite different and vary markedly from the corresponding unmodified interferon (Table 1). There are no significant differences in core parameters between male and female subjects, or among Black, Latino, and Caucasian patients with chronic HCV infection (PEGASYS[®]; Hoffmann-La Roche, Basel, Switzerland, 2004; PEG-Intron[®]; Schering Corporation, Kenilworth, NJ, 2005; Brennan et al., 2005).

PEG-IFN products are absorbed slowly. The absorption half-life for unmodified interferon-alpha and PEG-IFN-alpha-2a and -alpha-2b are 2.3, 50, and 4.6 hours,

Table 1 Pharmacokinetics of Unmodified and Pegylated Interferons

Peg-interferon	Peg-interferon alpha-2a	Interferon alpha	Peg-interferon alpha-2b	Reference
Absorption $t_{1/2}$ (h)	50	2.3	4.6	Glue et al. (2000a); Harris et al. (2001)
T_{max} (h)	45–81	7.3–12	16–44	Algranati et al. (1999); Glue et al. (2000a); Martin et al. (2000a, 2000b); Modi et al. (2000a); Wills (1990); Chatelut et al. (1999)
$T_{1/2}$ (h)	61–110	4–16	30–58	Algranati et al. (1999); Glue et al. (2000a, 2000b); Gupta et al. (2003); Martin et al. (2000b); Wills et al. (1990)
AUC	3334 ng · h/mL ^a	17,600pg · h/mL ^d	86,400pg · h/mL ^b	Glue et al. (2000a); Modi et al. (2000a); Wills et al. (1984)
V_d (L)	6–14	31–98	69.3 ^c	Glue et al. (2000a); Lamb & Martin (2002); Harris et al. (2001)
Cl/F	60–118 mL/h	4.9–21 L/h	22 mL/h/kg	Algranati et al. (1999); Glue et al. (2000a); Martin et al. (2000b); Modi et al. (2000a)

^a 180-µg/week multiple doses (subcutaneous injection);

^b 1.5-µg/kg/week (subcutaneous injection) measured at week 4;

^c based on a 70-kg person (0.99 L/kg);

^d 36×10^6 interferon alpha-2a (subcutaneous injection).

respectively (Harris et al., 2001; Glue et al., 2000). The time to achieve the maximum serum (T_{\max}) concentration is markedly increased by pegylation. The T_{\max} for unmodified interferon-alpha varies from 7.3 to 12 hours versus approximately 45 to 81 and 16 to 44 hours for PEG-IFN-alpha-2a and -alpha-2b in healthy adults and patients with compensated chronic HCV infection (Algranati et al., 1999; Glue et al., 2000; Wills, 1990; Wills et al., 1984; Chatelut et al., 1999; Martin et al., 2000, 2000a; Modi et al., 2000). Near-dose proportional maximum serum concentrations (C_{\max}) of PEG-IFN-alpha-2a are obtained approximately 80 hours after the first dose (Heathcote et al., 1999). Dose-related but not dose-proportional increases between the dose and C_{\max} are noted with PEG-IFN-alpha-2b (Glue et al., 2000, 2000a).

Absorption of PEG-IFN-alpha-2a has been shown to be particularly delayed in elderly males (mean T_{\max} = 116 hours) versus a mean of 81 hours in young males (Martin et al., 2000). Age does not affect the absorption of PEG-IFN-alpha-2b (Gupta et al., 2003). For children, limited data exist on the pharmacokinetics of PEG-IFN-alpha. Schwarz (2003) presented data on the absorption of PEG-IFN-alpha-2a after subcutaneous administration in 14 treatment-naïve HCV-infected children. The children received PEG-IFN-alpha-2a [(180 $\mu\text{g}/1.73 \text{ m}^2$) \times patient body surface area] for 48 weeks. Rapid and sustained absorption was noted after the first dose, with mean concentrations 24 and 96 hours after a dose of 22.3 ng/ml and 19.0 ng/ml, respectively. Steady-state concentrations were reached by week 12 of therapy.

The mean apparent volume of distribution (V_d) of unmodified interferon-alpha-2a and PEG-IFN-alpha-2a are markedly different, at 31 to 73 L and approximately 6 to 14 L, respectively (Harris et al., 2001; Lamb & Martin, 2002) (Table 1). In contrast, the mean apparent V_d for unmodified interferon-alpha-2b is approximately 98 L (1.4 liters/kg) versus 69.3 L (0.99 liters/kg) for PEG-IFN-alpha-2b for a 70-kg person (Glue et al., 2000). The volume of distribution of PEG-IFN-alpha-2a is also lower than unmodified and PEG-IFN-alpha-2b. The lower V_d for PEG-IFN-alpha-2a limits the distribution to well-perfused organs, allowing for a fixed-dose regimen (irrespective of body weight). On the other hand, the distribution of PEG-IFN-alpha-2b is closer to that of unmodified interferon.

Unmodified interferon-alpha is eliminated by glomerular filtration with reabsorption occurring in the proximal tubules (Wills, 1990). The liver plays a small part in the elimination of unmodified interferon-alpha. Additional catabolism may occur via interactions with cellular interferon receptors (Glue et al., 2000). In contrast, animal studies demonstrate that PEG-IFN-alpha-2a is metabolized mainly by the liver (Modi et al., 2000a). Non-renal clearance of PEG-IFN-alpha-2b accounts for approximately two-thirds of the total clearance (Gupta et al., 2002).

Unmodified interferon-alpha is rapidly eliminated from the body, with an average half-life between 4 and 16 hours (Glue et al., 2000; Wills, 1990). The mean apparent clearance varies from 4.9 to 21 liters/hour (Table 1) (Wills, 1990). Elimination half-lives for the PEG-IFN products are far longer. The mean half-life for PEG-IFN-alpha-2a varies from 61 to 110 hours, and the mean apparent clearance varies from 60 to 118 mL/hour in subjects with stable renal function. The mean half-life for PEG-IFN-alpha-2b is 30 to 58 hours (Table 1) (Glue et al., 2000, 2000a).

Steady-state concentrations of PEG-IFN-alpha-2a occur after 5–8 weeks of weekly administration (Modi et al., 2000).

Renal dysfunction affects the pharmacokinetics of PEG-IFNs differently (Martin et al., 2000a; Lamb et al., 2001; Gupta et al., 2002). For PEG-IFN-alpha-2a, the C_{\max} , distribution, and apparent total body clearance in subjects with stable chronic renal impairment were comparable to patients with normal renal function. Clearance (Cl/F) of PEG-IFN-alpha-2a was 25–45% lower in patients on hemodialysis, however, compared with subjects with normal kidney function (PEGASYS[®] package insert, 2004; Martin et al., 2000; Lamb et al., 2001). Dosage adjustment is recommended in patients with end-stage kidney disease on hemodialysis (PEGASYS[®] package insert, 2004).

In contrast, the C_{\max} and AUC (area under the concentration-time curve) increased up to two times in patients with decreased renal function receiving PEG-IFN-alpha-2b compared with patients with normal baseline renal function (Gupta et al., 2002). The mean half-life increased and the mean apparent body clearance decreased by 40% and 45%, respectively. Renal clearance accounts for approximately 30% of the total body clearance of PEG-IFN-alpha-2b. Patients with a calculated creatinine clearance less than 50 mL/min should receive PEG-IFN-alpha-2b therapy only after assessing the risks and benefits (PEG-Intron package insert, 2005).

As to removal of PEG-IFNs by hemodialysis, Barril (2004) performed an *in vitro* study comparing the effect of permeability and pore size of hemodialysis membranes on the blood levels of unmodified interferon-alpha-2a versus PEG-IFN-alpha-2a and PEG-IFN-alpha-2b. Pore size was more important than permeability in the removal of interferon products from the blood. Unmodified interferon and PEG-IFN-alpha-2b, but not PEG-IFN-alpha-2a, were cleared appreciably by membranes with middle to middle-large pore size (43–60 Å) high-flux dialysers. Given that PEG-IFN-alpha-2a is not as dependent upon renal clearance for elimination, it is the preferred choice for patients with renal dysfunction. In the case that a patient requires hemodialysis, PEG-IFN-alpha-2b may require supplemental dosing depending on the type of dialyser being used.

Concern about the effect of fixed dosing of PEG-IFN-alpha-2a in patients at the extremes of body weight has been raised. Although the drug has a low volume of distribution, morbidly obese patients may not achieve therapeutic interferon concentrations, while lighter patients may experience an increase in adverse events due to supratherapeutic levels. Obesity has been identified as an independent risk factor for nonresponse to unmodified and PEG-IFNs (Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001). It is unknown whether the decreased efficacy can be attributed to lower interferon levels, intrinsic resistance to the effects of interferon, or the presence of negative prognostic factors in obese patients (Swain et al., 2005). It has been reported that the C_{\max} and AUC of unmodified interferon are 35% and 25% lower in obese subjects versus non-obese patients (Lam et al., 1997). Bressler (2005) noted a 21% reduction in trough levels of PEG-IFN-alpha-2a in obese versus non-obese subjects receiving the 180- μ g dose. The trough concentrations after PEG-IFN-alpha-2a at 270 μ g/week were similar to those noted in the 180- μ g/week dose in non-obese subjects. In a single-dose study, the AUC for PEG-IFN-alpha-2a

and -2b was not related to body weight. However, the number of obese patients was small (Bruno et al., 2005). The significance of this finding will need to be determined in clinical trials. The manufacturer of PEG-IFN-alpha-2a is undertaking a study to determine the effectiveness of higher doses of PEG-IFN-alpha-2a in patients with HCV infection and who are over 85 kg (ClinicalTrials.gov Identifier: NCT00077649). Swain (2005) reported a higher incidence of serious adverse events in lighter patients (≤ 75.5 kg) receiving fixed-dose PEG-IFN-alpha-2a, but the number of withdrawals due to adverse events was not increased.

The pharmacokinetics of the two available PEG-IFNs vary. The decision to treat with one product over the other should take into consideration renal function and body size.

Drug Interactions

Drug-drug interactions for the PEG-IFNs are infrequent but are marked by consequence. Additive side effects are the most notable mechanism of interaction. Agents with similar adverse drug event profiles (e.g., hepatotoxins, or drugs that cause anemia) run highest on the list. As the metabolism and elimination of PEG-IFNs are not dependent on extensive oxidative metabolism, through any of the major cytochrome P450 enzyme systems, these agents are not subject to the inductive or inhibitory activity of other drugs. Additionally, neither PEG-IFN product exerts an effect on the majority of P450 enzyme systems, including 2C9, 2C19, 2D6, and 3A4 (Package insert, FDA Briefing Document, 2002). PEG-IFN-alpha-2a demonstrates mild inhibition of cytochrome P450 1A2, the enzyme responsible for metabolism of drugs such as theophylline, risperidone, clozapine, tricyclic antidepressants, and caffeine (FDA Briefing Document, 2002).

Treatment with PEG-IFN-alpha-2a once weekly for four weeks in healthy subjects taking theophylline was associated with a 25% increase in the total theophylline area under the concentration-time curve. The resultant effects were adverse effects of theophylline, including nausea, vomiting, palpitations, and seizures. The effect could be offset by a 25% reduction in the dose of theophylline. PEG-IFN-alpha-2a does not uniformly affect the disposition of methadone metabolism (Sulkowski et al., 2005a). Methadone exposure was increased by a mean of 10–15% in patients co-treated for four weeks. The levels of methadone doubled in two patients. No subject had clinical signs or symptoms of intoxication or withdrawal related to methadone. Mauss (2004) examined the effect of PEG-IFN-alpha-2b on 50 patients on methadone maintenance. While there was a high rate of discontinuation of therapy among this group of patients, there was no increase in adverse effects. RBV does not affect the disposition of PEG-IFN-alpha but contributes significantly to the untoward effects on hematological counts, particularly red blood cells (RBC).

Directly hepatotoxic agents used in combination with PEG-IFN can elicit additive drug toxicity. Concomitant use of the nonnucleoside reverse transcriptase inhibitor nevirapine, a known hepatotoxin, has been associated with a higher

incidence of advanced liver fibrosis (Macias et al., 2004). Numerous case reports and retrospective reviews identify didanosine, when used in combination with PEG-IFN products with ribavirin, as a prominent risk factor for cases of fatal hepatic failure, peripheral neuropathy, pancreatitis, and lactic acidosis (Bani-Sadr et al., 2005). Use of ritonavir or ritonavir plus saquinavir in HIV patients infected with the hepatitis C or B virus has also been associated with increased rates of severe hepatotoxicity.

PEG-IFNs, in combination with RBV, may additionally antagonize stavudine and zidovudine antiretroviral activity, secondary to inhibition of intracellular phosphorylation. Use of alternate antiretroviral agents is recommended. For all co-infected patients (HCV and HIV infection), increased vigilance for signs of hepatotoxicity is highly recommended.

Mechanism of Action

PEG-IFNs were developed in order to achieve a more sustained antiviral and immunodulatory effect than unmodified interferon (Kamal et al., 2002). Their mechanism of action is the same as for unmodified interferon. The chapter by Dr. Dash in this manuscript provides extensive insight into the mechanism of interferon action and resistance.

PEG-IFN-alpha combined with RBV is the recommended treatment for the management of patients with chronic HCV infection (National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C, 2002). When combined with PEG-IFN, RBV significantly improves the possibility of achieving an SVR in patients with chronic HCV infection when compared with an interferon-alpha by itself, therapy with RBV, or PEG-IFN-alpha alone (Fried et al., 2002; Manns et al., 2001). When used as monotherapy in patients with chronic HCV infection, RBV has been shown to improve serum alanine aminotransferase (ALT) concentrations (Bodenheimer et al., 1997; Dusheiko et al., 1996). No significant decrease in HCV RNA concentrations were noted during therapy. On the other hand, Pawlotsky (2004) noted a moderate (-0.5 to $-1.6 \log_{10}$) but transient (days 2 and 3 and disappearing by day 4) decrease in HCV RNA concentrations in 4 of 7 subjects receiving monotherapy with RBV.

The exact mechanism of action of RBV when combined with interferon-alpha therapy is unknown. The chemical structure of RBV is depicted in Figure 2. Several hypotheses have been proposed. RBV may act by inhibiting DNA, RNA, and protein synthesis, leading to a decrease in production of pro-inflammatory cytokines such

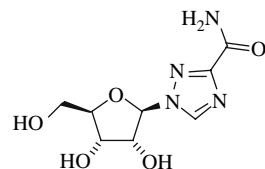


Fig. 2 Ribivirin

as interferon- γ and may induce apoptosis of cells in the inflammatory infiltrate in the infected liver (Meier et al., 2003). Modulation of the T helper 1/Th2 cytokine-mediated immune response with an emphasis on the type 1 cytokine profile is consistent with the results of combined therapy with PEG-IFN-alpha-2a (Kamal et al., 2002; Tam et al., 1999; Hultgren et al., 1998). The mutagenic activity of RBV on HCV is also a possible mechanism (Asahina et al., 2005).

Pharmacodynamics

Administration of unmodified interferon-alpha or PEG-IFN-alpha products results in a multiphase decline of HCV RNA concentrations. A study by Zeuzem (2001) noted a rapid first-phase decline in HCV RNA concentrations in 79% and 76% of patients receiving unmodified interferon and PEG-IFN-alpha-2a, respectively. This response was noted within 48 hours of initiation of interferon therapy. The first phase of viral decline is thought to reflect an interferon-induced blockade of virus production or release, as well as the degradation rate of free virus (Neumann et al., 1998). After about 24 to 48 hours, the viral decline slows and a second phase of HCV RNA decay is noted. The second-phase decline is thought to reflect the degradation rate of infected cells or the elimination of virus from infected hepatocytes (Neumann et al., 1998; Lutchman & Hoofnagle, 2003). The decrease in HCV RNA concentrations was faster in both phases in patients infected with a non-1 HCV genotype (Zeuzem et al., 2001). The degree of second-phase decline of HCV RNA was predictive of SVR (Zeuzem et al., 2001). A similar pattern of HCV RNA decline has been noted in patients who are infected with HCV genotype 1 and receive PEG-IFN-alpha-2b (Buti et al., 2002).

Herrmann (2003) studied the effect of the addition of RBV on the viral kinetics of unmodified interferon-alpha-2b and PEG-IFN-alpha-2a in patients with genotype 1 chronic hepatitis C infection. In addition to the two phases reported by Zeuzem (2001), they noted a third phase of viral decay in 57%, 56%, and 89% of patients receiving unmodified interferon-alpha-2b with RBV and PEG-IFN-alpha-2a without and with RBV, respectively. The third phase of viral decline began at day 7 to day 28 after initiation of therapy. The third-phase kinetic parameters were predictive of an end-of-treatment response (ETR—undetectable HCV RNA concentrations at the end of 48 weeks of therapy) ($P = 0.001$) but not SVR ($P = 0.11$). This third phase was attributed to a treatment-enhanced loss of HCV-infected cells. Pawlotsky (2002) and Neumann (2002) found that a triphasic HCV RNA decay pattern was more common in HCV genotypes 4 and 1 (38%) versus genotypes 2 and 3 (3%). All genotype 1 patients who had a bi-phasic response to PEG-IFN-alpha-2a plus RBV had a rapid viral response (RVR) (a second slope greater than 0.3 IU/ml/week), whereas only 62% of those with a tri-phasic response had an RVR.

Zeuzem (2005) investigated whether individualizing therapy for chronic HCV-infected patients based on viral responses to treatment increased the likelihood of achieving an SVR. An SVR was defined as an undetectable serum HCV RNA (<50

IU/mL) 24 weeks after the end of therapy. Study results indicated that individualized therapy was no better than standard therapy in the management of patients.

Therapeutic Efficacy

Determination of genotype is the first step in the consideration of treatment with either of the PEG-IFNs. This will help determine the length of therapy and the likelihood of treatment success, aiding the patient and provider in the benefit versus risk analysis. Patients infected with genotype 2 or 3 respond better to therapy than subjects infected with genotype 1 or 4 (National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C, 2002; Sherman et al., 2004)

Monotherapy with PEG-IFN-Alpha

Combination therapy with PEG-IFN and RBV is the therapy of choice for the management of HCV infection. However, in those situations where the patient is intolerant or has a contraindication to the use of RBV, monotherapy with PEG-IFN is indicated. Four randomized controlled trials in interferon-naïve subjects with chronic HCV infection demonstrated the superiority of treatment with PEG-IFN-alpha-2a over unmodified interferon-alpha-2a (Reddy et al., 2001; Heathcote et al., 2000; Zeuzem et al., 2000; Pockros et al., 2004). A sustained biochemical response, end-of-treatment virological response, sustained virological response, and histological response were therapeutic endpoints. A sustained biochemical response was defined as a normal serum ALT at week 72, and a histological response was defined as a ≥ 2 -point decrease in the total histological activity index (HAI) in liver biopsy results between baseline and week 72. An end-of-treatment virological response and a sustained virological response were defined as an undetectable plasma HCV RNA after 48 weeks of therapy and an undetectable HCV RNA concentration (<100 copies/mL) at week 72, respectively.

The specific relative rates of response are summarized in Table 2. For all therapeutic endpoints, a statistically significant benefit was seen with treatment with PEG-IFN-alpha-2a over unmodified interferon. The greatest relative benefit for all parameters was noted with treatment at the highest dose, of 180 $\mu\text{g}/\text{week}$. The 135- $\mu\text{g}/\text{week}$ dose achieved an identical SVR as the 180- $\mu\text{g}/\text{week}$ dosing regimen, but the histological response was inferior and no different from that of unmodified interferon-alpha-2a (Pockros et al., 2004). The histological response correlates to SVR (Reddy et al., 2001; Heathcote et al., 2000; Zeuzem et al., 2000; Cammà et al., 2004). A histological response, however, was found in some patients who failed to respond to therapy or who relapsed after an end-of-treatment response (Heathcote et al., 2000). These data indicate that therapy with PEG-IFN can have a beneficial effect even without an SVR.

Table 2 Monotherapy with Unmodified Versus Peg-Interferon-Alpha in Patients with Chronic HCV Infection

Medication	Sustained Biochemical Response (%)	P value	End of Treatment Virologic Response (%)	P value	Sustained Virologic Response (%)	P value
Unmodified interferon alpha-2a ^{a,b}	9	$P = 0.004$	12	$P = 0.0002$	3	$P = 0.0006$
Peginterferon alpha-2a 180 µg/week ^c	38		60		36	
Unmodified interferon alpha-2a ^{b,c,d}	15	$P = 0.004$	14	$P = 0.0010$	8	$P = 0.0010$
Peginterferon alpha-2a 180 µg/week ^c	34		44		30	
Unmodified interferon alpha-2a ^{c,e,f}	25	$P = 0.001$	28	$P = 0.0010$	19	$P = 0.0010$
Peg-interferon alpha-2a 180 µg/week ^c	45		69		39	
Unmodified interferon alpha-2a ^{b,c,g}	18	$P = 0.001$	22	$P = 0.0010$	11	$P = 0.0010$
Peg-interferon alpha-2a 135 µg/week ^c	32		53		28	
Peg-interferon alpha-2a 180 µg/week ^c	32		55		28	
Unmodified interferon alpha-2b ^{b,c,h}	NA	NA	24		12	$P < 0.0010$
Peg-interferon alpha-2b 1.0 µg/kg/week ^c	NA		41		25	
Peg-interferon alpha-2b 1.5 µg/kg/week ^c	NA		49		23	

^a Reddy et al. (2001);

^b 3 million units three times weekly for 48 weeks;

^c 48 weeks of therapy;

^d Heathcote et al. (2000);

^e 6 million units for 12 weeks then 3 million units for 36 weeks;

^f Zeuzem et al. (2000);

^g Pockros et al. (2004);

^h Lindsay et al. (2001).

The likelihood of achieving an SVR was lower in patients infected with HCV genotype 1 when compared to non-1 genotypes. The chance of achieving an SVR in patients infected with HCV genotype 1 varied from 12–31% (180 µg PEG-IFN-alpha-2a weekly for 48 weeks) versus unmodified interferon-alpha-2a (2–7%) (Reddy et al., 2001; Heathcote et al., 2000; Pockros et al., 2004; Zeuzem et al., 2000). In patients infected with HCV non-1 or unknown genotype, the response was approximately 41–51% in the 180-µg/week PEG-IFN-alpha-2a groups versus 0–19% for unmodified interferon-alpha-2a (Reddy et al., 2001; Heathcote et al., 2000; Pockros et al., 2004).

Lindsay (2001) performed a randomized, double-blind study (for PEG-IFN-alpha-2b doses) comparing PEG-IFN-alpha-2b with unmodified interferon-alpha-2b in interferon-naïve patients with chronic HCV infection (Table 2). An end-of-treatment virological response was recorded in 24%, 41%, and 49% of patients receiving unmodified interferon, PEG-IFN-alpha-2b (1.0 µg/kg/week), and PEG-IFN-alpha-2b (1.5 µg/kg/week), respectively. The end-of-treatment virological response was statistically greater for all of the PEG-IFN dosing groups when compared with unmodified interferon ($P < 0.001$). The SVR for the 1.0-µg/kg/week (25%) and 1.5-µg/kg/week (23%) doses of PEG-IFN-alpha-2b were identical and significantly different from unmodified interferon-alpha-2b (12%) ($P < 0.001$ for both PEG-IFN doses).

Combination Therapy with PEG-IFN Alpha-2a and RBV

Major randomized controlled trials have been used to develop consensus guidelines for the use of PEG-IFN combined with RBV for the management of patients with chronic HCV infection (Manns et al., 2001; Fried et al., 2002; Hadziyannis et al., 2004). Like monotherapy, the treatment duration and the likelihood of achieving an SVR are determined by HCV genotype. In this section, we will review the available information concerning the treatment of chronic HCV genotypes 1–6.

Overall SVR and SVR by genotype results are listed in Table 3. Combination therapy with PEG-IFN plus RBV generally exceeds monotherapy and combination therapy with unmodified IFN in terms of the SVR rates ($P = 0.01$, Manns et al., 2001; $P < 0.001$, Fried et al., 2002). The overall SVR in patients receiving PEG-IFN-alpha plus RBV for 48 weeks varied in these trials from 54–63%. The dose of RBV studied was from 800 mg daily in the Manns study (2001) to between 1–1.2 g daily based on body weight in other major studies (Fried et al., 2002; Hadziyannis et al., 2004).

Manns (2001) suggest that higher doses of RBV can maximize response. In their randomized, open-label trial, they noted that the likelihood of achieving an SVR was higher for all genotype groups in patients receiving higher RBV doses, between 10.6–15 mg/kg per day. From this finding and the desire to determine if the results from controlled randomized studies could be replicated in a community setting, the WIN-R study (Jacobson et al., 2005) was designed. This study was a U.S. community-based trial enrolling 4,913 patients. The relative benefit of combining 1.5 µg/kg/week of PEG-IFN-alpha-2b with either a fixed dose (FD 800 mg/day) or

Table 3 Efficacy of (Combination Therapy) PEG-IFN Plus RBV in Subjects with Chronic HCV Infection

Regimen	SVR	SVR	SVR
	Overall (%)	Genotype 1 (%)	Genotype 2 or 3 (%)
Interferon alpha-2b plus RBV (1–1.2 g/day) (48 weeks) ^a	47	33	79
PEG-IFN alpha-2b 1.5 µg/kg/week plus RBV 800 mg daily (48 weeks)	54	42	82
PEG-IFN alpha-2b 1.5 µg/kg/week then 0.5 µg/kg/week plus RBV 1–2 g daily (48 weeks) ^b	47	34	80
Interferon alpha-2b plus RBV 1–1.2 g/day (48 weeks) ^c	44	36	61
PEG-IFN alpha-2a 180 µg/week plus placebo (48 weeks)	29	21	45
PEG-IFN alpha-2a 180 µg/week plus RBV 1–1.2 g/day (48 weeks)	56	46	76
PEG-IFN alpha-2a 180 µg/week plus RBV 800 mg/d (24 weeks) ^d	NA	29	84
PEG-IFN alpha-2a 180 µg/week plus RBV 1–1.2 g/d (24 weeks)	NA	41	81
PEG-IFN alpha-2a 180 µg/week plus RBV 800 mg/d (48 weeks)	NA	40	79
PEG-IFN alpha-2a 180 µg/week plus RBV 1–1.2 g/d (48 weeks)	63	52	76

^a Manns et al. (2001);

^b 1.5 µg/kg/week PEG-IFN alpha-2b for 4 weeks followed by 0.5 µg/kg/week for 44 weeks;

^c Fried et al. (2002);

^d Hadziyannis et al. (2004), PEGASYS®; Hoffmann-La Roche, Basel, Switzerland, 2004.

a weight-based dose (WBD 800–1400 mg/day) of RBV was examined. Treatment-naïve patients infected with HCV genotype 1 received 48 weeks of therapy, and patients with HCV genotype 2 or 3 received either 24 or 48 weeks of therapy. The overall SVR in the WBD and FD groups was 44% and 41%, respectively ($P = 0.02$). These results were lower than those reported by Manns (2001) (54%) utilizing a similar protocol with fixed-dose RBV. This may have been a reflection of the greater need for dose reductions of RBV in the WBD group due to anemia. Afdhal (2006) investigated the influence of RBV dose and the presence of liver fibrosis and cirrhosis on SVR in the WIN-R trial. With advanced histological changes, specifically patients classified at Metavir stage 3 to 4, SVR rates were significantly better for patients receiving the weight-based dose versus the fixed dose of RBV (43% versus 37%, $P = 0.02$). Patients with cirrhosis had the lowest overall SVR (34%) when compared with subjects with stages 0–3 (44–46%) ($P < 0.0001$).

Genotype 1

When analyzing the response in HCV genotype 1 infected patients receiving combination therapy with PEG-IFN-alpha plus RBV for 48 weeks, response rates varied from 42–52% (Manns et al., 2001; Fried et al., 2002; Hadziyannis et al., 2004).

Combination PEG-IFN plus RBV regimens are significantly better than unmodified interferon/RBV combinations ($P = 0.02$, Manns et al., 2001; $P = 0.01$, Fried et al., 2002). An even higher rate of response was noted by Sakai (2006), at 61% in treatment-naïve Japanese patients infected with HCV genotype 1b. Post hoc subgroup analyses, by Fried (2002) and Hadziyannis (2004) and Zarski (2005), demonstrate a significantly greater chance of achieving an SVR in patients infected with HCV genotype 1b (53%) versus 1a (45%) ($P = 0.004$).

Even lower rates of treatment success were reported in the community-based trial, WIN-R, wherein SVRs in patients infected with HCV genotype 1 were 34% (WBD) and 29% (FD) ($P = 0.004$) (Jacobson et al., 2005). Subjects with a low viral load (< 2 million copies/mL) had a greater likelihood of experiencing an SVR than patients with a high viral load (≥ 2 million copies/mL), 35% versus 31%, $P = 0.006$ (Jacobson et al., 2006).

Hadziyannis (2004) studied the effect of treatment duration and RBV dose on the likelihood of achieving an SVR in HCV genotype 1 infected patients. They found a significant correlation with SVR in patients treated for 48 weeks versus those treated for 24 weeks ($P < 0.001$). They also reported a significant effect of weight-based RBV versus low-dose RBV (800 mg daily) on the achievement of an SVR ($P = 0.005$). Subjects with bridging fibrosis or cirrhosis responded best to weight-based RBV and 48 weeks of therapy.

Genotype 2 or 3

The SVR for patients infected with genotype 2 or 3 varied between 76–82% in patients receiving PEG-IFN-alpha/RBV for 48 weeks (Table 3) (Manns et al., 2001; Fried et al., 2002; PEGASYS®; Hoffmann-La Roche, Basel, Switzerland, 2004). Hadziyannis (2004) found no difference in the achievement of an SVR in patients infected with genotype 2 or 3 based on length of therapy or RBV dose ($p > 0.2$ for both). In fact, the 24-week regimen (800-mg dose of RBV) had the highest SVR (84%). Manns (2001) reported no differences in SVR between PEG-IFN-alpha-2b/RBV study groups and unmodified interferon/RBV in patients infected with genotype 2 or 3 treated for 48 weeks.

In the community-based WIN-R study, fixed-dose RBV (800 mg/day) was as equally effective as WBD RBV (800–1400 mg daily) in inducing an SVR in patients with chronic HCV genotype 2 or 3 infection (60% versus 62%, $P = 0.26$) (Jacobson et al., 2005). Patients with genotype 2 had a higher SVR than those with genotype 3 (72% versus 63%) (Brown et al., 2006). The authors suggested that patients infected with HCV genotype 3 may benefit from WBD of RBV.

Zeuzem (2004) performed a phase 4 study to investigate the safety and efficacy of treatment for 24 weeks with 1.5 $\mu\text{g}/\text{kg}/\text{week}$ of PEG-IFN-alpha-2b with weight-based RBV (800–1,400mg/day) in patients infected with HCV genotype 2 or 3. The overall SVR was 81%, and the SVR for HCV-2 and HCV-3 was 93% and 79%, respectively. The reduced SVR in patients infected with HCV genotype 3 was attributed to the presence of a high baseline viral load and high-grade hepatic

steatosis. The authors raised the question of whether patients infected with HCV-3 with poor prognostic factors should be treated for longer than 24 weeks. Controlled studies will be necessary to answer this question.

Genotype 4

Hepatitis C virus genotype 4 is more common in Africa and eastern Mediterranean countries and has a prevalence of 60% in Saudi Arabia and up to 90% in Egypt. Fried (2001) and Hadziyannis (2004) noted SVR rates in HCV genotype 4 infected patients receiving PEG-IFN-alpha-2a plus weight-based RBV for 48 weeks at 77–82%. The study size was small, however. Khuroo (2004) performed a meta-analysis of available trials of PEG-IFN-alpha plus RBV for the management of chronic HCV genotype 4 infection. They reported an overall predicted SVR rate of 72% in patients treated for 48 weeks with PEG-IFN-alpha (2a: 180 µg/week; or 2b: 1.5 µg/kg/week) and RBV (1–1.2 g/day based on body weight). Trials utilizing these guidelines have reported SVR values between 61–69% (Elmakhzangy et al., 2005; Hasan et al., 2004; Kamal et al., 2005). Kamal (2005) investigated the effect of the duration of therapy on the achievement of an SVR in patients infected with HCV genotype 4. Patients were randomized to receive PEG-IFN-alpha-2b (1.5 µg/kg/weekly) with RBV (1–1.2 g/day) for 24, 36, or 48 weeks. An SVR occurred in 24%, 66%, and 69% of patients treated for 24, 36, and 48 weeks, respectively. No statistical difference was found between 36 or 48 weeks of therapy ($P = 0.3$). The 36- and 48-week regimens were statistically different when compared to the 24-week arm of the study ($p < 0.001$, for both). An early virological response at 12 weeks was predictive of an SVR as long as therapy was at least 36 weeks in duration. The authors concluded, however, that patients with high baseline HCV RNA viral loads may do better with 48 weeks of therapy.

Genotype 5 or 6

Much less data exist on the management of patients infected with chronic HCV genotype 5 or 6. In a retrospective review of patients with HCV genotype 5 infection, D'Heygere (2005) reported an SVR of 55%. Patients were treated for 48 weeks with 180 µg/week of PEG-IFN-alpha-2a and RBV (1–1.2 g/day). Bonny (2005) reported an SVR similar to that of unmodified interferon (64%), in treatment-naïve patients infected with HCV genotype 5, receiving PEG-IFN-alpha-2b or PEG-IFN-alpha-2a plus RBV (60%). Both regimens were administered for 48 weeks. Nguyen (2003) reported an SVR of 54% in patients treated with peginterferon/ribavirin for 24 weeks. The SVR rate in two small studies of HCV genotype 6 infected individuals utilizing unmodified interferon/ribavirin were 79% and 62.5%, respectively (Dev et al., 2002; Hui et al., 2003). Therapy duration was 52 and 48 weeks, respectively. A study to determine the ideal length of therapy in patients infected with

HCV genotype 6 receiving peginterferon-alpha-2b/ribavirin therapy is under way (ClinicalTrials.gov Identifier: NCT00255008).

Comparative Efficacy Between Pegylated Products

To date, there have been no large head-to-head trials evaluating the safety and/or efficacy between the two products. As of preparation of this chapter, the manufacturer of PEG-IFN-alpha-2b (Schering-Plough) is funding a head-to-head safety and efficacy trial of the two PEG-IFN products entitled the “Individualized Dosing Efficacy Versus Flat Dosing to Assess Optimal Pegylated Therapy (IDEAL) Trial.” Treatment-naïve patients infected with HCV genotype 1 are being randomized to receive PEG-IFN-alpha-2b at a dose of 1.0 or 1.5 µg/kg/week plus weight-based RBV (800–1,400 mg/day) or 180 µg/week PEG-IFN-alpha-2a with RBV (1–1.2 g/day) for a total of 48 weeks. The primary endpoint of the study will be the SVR rate. One concern about the design of the study is the way the protocol deals with alterations in the RBV dose. Patients in the PEG-IFN-alpha-2b arms will have a two-step dose reduction process. If necessary, the dose of RBV will be decreased to between 600 and 1,000 mg depending on the starting dose. If necessary, the dose may be reduced by another 200 mg. In contrast, for the PEG-IFN-alpha-2a group, the dose is reduced to 600 mg/day. Since it is known that the RBV dose is extremely important to the achievement of an SVR, the study design could reflect a bias in favor of PEG-IFN-alpha-2b.

Importance of Completing the Therapeutic Regimen

Ferenci (2005) investigated the importance of completing the prescribed regimen with PEG-IFN-alpha-2a and RBV on the likelihood of achieving an SVR in patients infected with HCV genotype 1. Patients who received $\geq 80\%$ of the prescribed RBV dose experienced a greater chance of having an SVR than those who received $< 80\%$. The SVR rate was also lower in patients who received $\geq 80\%$ of the prescribed PEG-IFN-alpha dose but less than 80% of the RBV dose when compared with subjects who completed $\geq 80\%$ of the RBV dose (48% vs. 69%, $P = 0.014$). Patients who completed $\geq 80\%$ of both PEG-IFN and ribavirin had the lowest SVR (29%). Ribavirin dose changes after 24 weeks in patients infected with HCV genotype 2 or 3 had no effect on SVR rates. Shiffman (2004) found similar results in a retreatment study in patients who had failed previous unmodified interferon-based therapy. In this trial, the reduction of the PEG-IFN-alpha-2a dose during the first 20 weeks of therapy did not greatly affect SVR. However, the reduction of the RBV dose from $> 80\%$ to $< 60\%$ of the target dose during the first 20 weeks did significantly reduce the SVR rate (21% vs. 11%, $P = 0.03$). Decreases in dosages of either medication had little effect on SVR after 20 weeks of therapy.

Predictors of Response and Duration of Therapy

Significant predictors of SVR (by multiple regression analysis) for patients receiving monotherapy with PEG-IFN-alpha-2a include the following baseline parameters: genotype non-1, serum HCV RNA levels < 2 million copies/mL, absence of cirrhosis, alanine aminotransferase quotient (ALT) > 3 (average ALT values prior to therapy, divided by the upper limit of normal), body weight < 85 kg, age < 40 years, and HAI > 10 (histological activity index) (Lee et al., 2002). Race and gender were not statistically significant predictors in this review. In contrast, logistic regression analysis of baseline characteristics in patients receiving PEG-IFN-alpha-2b revealed only two significant predictive factors (an HCV genotype other than 1 and an HCV RNA viral load ≤ 2 million copies/mL serum) (Lindsay et al., 2001).

Lee (2002) performed an analysis of outcomes in patients with chronic HCV infection receiving peginterferon-alpha-2a monotherapy to determine the predictive value of periodic HCV RNA concentrations for the achievement of an SVR. Patients with an undetectable HCV RNA (< 100 copies/mL) or a ≥ 2 \log_{10} drop in viral load from baseline at week 12 (EVR: early virological response) showed a negative predictive value of 0.98. Accordingly, if a patient does not achieve an EVR by week 12, only 2% of subjects would achieve an SVR. It is important to note that due to assay variability, the measured HCV RNA concentration may vary up to 0.5 \log_{10} . The issue should be considered when making decisions about stopping or continuing therapy. From these data, for patients receiving monotherapy with peginterferon-alpha for chronic HCV infection, decisions on whether to continue or stop therapy should be based on the HCV RNA concentration at week 12 of therapy utilizing the EVR criteria (National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C, 2002).

For combination therapy, multiple logistic regression analysis revealed only three baseline factors associated with a significant likelihood of achieving an SVR in patients receiving PEG-IFN-alpha-2a with RBV (Fried et al., 2002). These are a non-1 HCV genotype, age ≤ 40 years of age, and weight ≤ 75 kg. Manns (2001) performed a similar analysis of significant predictors of SVR in subjects receiving PEG-IFN-alpha-2b and RBV. These are a non-1 HCV genotype, a lower baseline viral load, lighter weight, younger age, and absence of bridging fibrosis/cirrhosis. Significant factors predictive of an SVR in patients with HCV genotype 2 or 3 were treatment duration of at least 16 weeks, baseline HCV RNA concentrations, and hepatic steatosis less than 5% (Zeuzem et al., 2004). For patients infected with HCV genotype 4, Kamal (2005) identified, by multivariate analysis, viral load (≤ 2 million copies/mL), age ≤ 40 years, and therapy duration as significant predictors of an SVR.

Davis (2002) reviewed two studies using PEG-IFN-alpha-2a or -2b plus RBV to determine whether an early virological response to therapy could predict the likelihood of achieving an SVR and be used to develop early stopping rules for therapy. The early virological response (EVR) that had the best negative predictive value for SVR (98.4%) was determined to be a fall in HCV RNA from baseline by ≥ 2 \log_{10} units or an undetectable level as measured by a quantitative PCR method

at 12 weeks of therapy. Therefore, if therapy was discontinued in those patients who had not demonstrated an EVR, 1.6% of subjects would have achieved an SVR had therapy continued. Subgroup analysis by HCV genotype also showed that the above definition of EVR was applicable regardless of infection with genotype 1 or genotype 2 or 3. The negative predictive value for patients infected with genotype 1 or genotype 2 or 3 was 99% and 91%, respectively. The author recommended that patients infected with genotype 1 who achieve an EVR at 12 weeks should complete a full 48 weeks of combination therapy. Subjects who do not achieve an EVR should have therapy discontinued. If an EVR is achieved but HCV RNA is still detectable, patients should be retested at 24 weeks and, if still positive for HCV RNA using a sensitive qualitative PCR method, therapy should be discontinued. Patients infected with HCV genotype 2 or 3 need not undergo viral load testing at 12 weeks and should automatically be treated for a total of 24 weeks. Caution should be used in extrapolating these findings to other HCV-infected patient populations.

Efficacy of Longer Treatment Duration

Clinical trials have been performed to determine if prolonging therapy with PEG-IFN plus RBV has an effect on SVR rates over the current 54–63%. Berg (2006) randomized treatment-naïve patients infected with HCV genotype 1 into two groups. Group A received PEG-IFN-alpha-2a (180 µg/weekly) plus RBV (800 mg daily) for 48 weeks, and Group B received the same regimen for 72 weeks. Patients were followed for 24 weeks after therapy completion. Study results showed no advantage for prolonging therapy in the overall population. The overall SVR for Groups A and B were 53% and 54%, respectively. Subgroup analysis did show an advantage for 72 versus 48 weeks of therapy in subjects who were HCV RNA positive at week 12 (SVR, 29% vs. 17%, $P = 0.04$). Relapse rates were lower in subjects with a slow virological response in Group B versus Group A who became HCV RNA negative for the first time at week 12 or 24. Patients with an EVR (undetectable HCV RNA concentrations at 4 or 12 week) had SVR rates between 76–84%. The duration of treatment was not a factor in these subjects. Although adverse events were similar in severity and incidence, discontinuation rates were greater in Group B. The authors recommend that prolonged therapy be reserved for patients infected with HCV genotype 1 who are HCV RNA positive at therapy week 12 but with undetectable concentrations at week 24 of therapy.

Sánchez-Tapias (2006) investigated whether extending the duration of therapy in patients with detectable HCV RNA concentrations at week 4 of therapy (RVR) would improve SVR rates in subjects with chronic HCV infection. Patients received the same dosing regimen of PEG-IFN-alpha-2a and RBV as mentioned above. Patients without an RVR were randomly assigned to receive either 48 weeks (Group A) or 72 weeks (Group B) of therapy and 24 weeks of followup. The overall SVR rates for Group A and Group B were 32% and 45%, respectively ($P = 0.01$). Although the end-of-treatment response was identical in both groups (61%), the relapse rate was significantly higher in Group A versus Group B (48% and 26%,

respectively). In patients with HCV genotype 1 infection, the SVR was 28% (Group A) and 44% (Group B) ($P = 0.003$). As in the study by Berg (2006), the dropout rate was higher in the 72-week versus the 48-week group. Both studies by Berg (2006) and Sanchez-Tapias (2006) indicated that it is difficult for patients to complete 72 weeks of therapy. The RBV dose used in these studies was low when compared to current standards, and this may have influenced response to therapy. More study will be necessary to determine the value of prolonging PEG-IFN-alpha therapy utilizing weight-based ribavirin (i.e., 1–1.2 g/daily) in HCV-infected patients with a slow virological response to therapy.

Use of Rapid Virological Response at 4 Weeks to Determine Shorter Duration of Therapy in Select Groups of Patients with Chronic HCV Infection

Investigations into the possibility of treating select patients for a shorter period of time have been undertaken. Shorter duration of therapy with equal efficacy has the advantage of increased cost efficiency and potentially reduced adverse drug events. Zeuzem (2006) performed a study to investigate whether 24 weeks of PEG-IFN-alpha-2b plus RBV (weight-based) would be as effective as 48 weeks (historical control group) in patients infected with chronic HCV genotype 1 and low baseline HCV RNA concentrations ($\leq 600,000$ IU/mL). When SVR was compared, the 24-week regimen (50%) was inferior to the 48-week regimen (69%). Subgroup analysis, however, showed that those subjects with undetectable serum HCV RNA after 4 weeks of therapy (rapid virological response, RVR) had an SVR rate of 89%. If the serum HCV RNA was undetectable after both 4 and 24 weeks of therapy, the SVR was 92%. Liver biopsy revealed the presence of mild inflammation and an average Knodell fibrosis score of 1.2. Adverse events that led to the discontinuation of therapy or dose reduction were less in the 24-week study compared to rates during the initial 24 weeks and 48 weeks in the historical control group.

Jensen (2006) performed a retrospective analysis reviewing the association between an RVR at 4 weeks and SVR in patients receiving PEG-IFN-alpha-2a with RBV, infected with HCV genotype 1. They utilized data from the Hadziyannis study (2004). The primary focus of the analysis was on those patients who achieved an SVR after 24 weeks of therapy and had an RVR. Of the patients treated for 24 weeks, 24% achieved an RVR. Eighty-nine percent of patients with an RVR at 4 weeks achieved an SVR after 24 weeks of therapy versus 19% without an RVR. The authors compared the length of therapy and noted no difference in SVR in patients with an RVR at 4 weeks treated for 24 or 48 weeks. Multiple logistic analyses revealed an RVR at 4 weeks and baseline HCV RNA concentration ($< 2,000,000$ IU/mL versus $> 600,000$ IU/mL, $P < 0.026$) correlated with an SVR. It is important to note that only 7% and 18% of subjects in this study had cirrhosis or bridging fibrosis on liver biopsy, respectively. Whether these results can be extrapolated to patients with more severe liver disease is unknown. Ferenci (2006) reported a 75%

SVR in patients (HCV genotype 1 or 4) treated with PEG-IFN-alpha-2a and RBV for 24 weeks and an RVR at 4 weeks of therapy. In this prospective study, patients with an SVR had lower baseline HCV RNA concentrations than those who relapsed after an end-of-therapy response.

The European Medicines Agency (EMA) has approved short-course therapy (24 weeks) of combined PEG-IFN-alpha-2b (1.5 µg/kg/week) plus RBV (800–1,200 mg/daily) in patients with chronic HCV genotype infection with low viral HCV load. Patients must also have an undetectable serum HCV RNA at 4 and 24 weeks of therapy.

Trials to investigate the efficacy of a shorter duration of therapy for the patients with HCV genotype 2 or 3 who experience an RVR after 4 weeks of PEG-IFN-alpha-2b or -2a combined with RBV have been performed. In the study by Mangia (2005), patients received 1.0 µg/kg/week PEG-IFN-alpha-2b plus RBV 1–1.2 g daily via a randomization to one of two groups. Group 1 received therapy for 24 weeks. Patients who experienced an RVR at 4 weeks (Group 2) received therapy for 12 weeks, and subjects who did not have an RVR were treated for 24 weeks. Overall, patients in Group 1 and Group 2 that had an RVR had an SVR rate of 91% and 85%, respectively. Patients with an RVR infected with genotype 2 had an SVR rate of 89% and 87% in Groups 1 and 2, respectively. Although the SVR rate in patients infected with HCV genotype 3 who achieved an RVR was not statistically different, the response was 100% in Group 1 ($n = 10$) and 77% in Group 2 ($n = 24$).

Von Wagner (2005) performed a similarly designed study in patients infected with chronic HCV genotype 2 or 3 who received PEG-IFN-alpha-2a (180 µg/week) plus RBV (800–1,200 mg daily). Patients were treated for 4 weeks, and those subjects with an undetectable HCV RNA (RVR) were allocated to receive a total of 16 (Group A) or 24 weeks (Group B) of therapy. Subjects with detectable HCV RNA concentrations at 4 weeks received 24 weeks of therapy (Group C). An SVR was achieved in 82% and 80% of patients in Groups A and B, respectively. Interestingly, subjects without an RVR (Group C) had an SVR of 36% versus 81% in Group B even though both groups received therapy for 24 weeks. As in the study above, the SVR for subjects infected with HCV genotype 2 was greater than in those with HCV genotype 3, 92% versus 73%. Baseline viral load did not affect the SVR rate for patients with HCV genotype 2. However, a baseline viral load >800,000 IU/mL significantly affected the SVR rate in patients infected with genotype 3 compared with lower viral loads ($P = 0.003$). Patients infected with HCV genotype 3 and a baseline viral load >800,000 IU/mL experienced a higher SVR rate when treated for 24 weeks than 16 weeks, although the difference was not statistically different ($P > 0.2$). These results strongly favor a shorter duration of therapy in patients infected with HCV genotype 2 who experience an RVR to therapy. The results in patients infected with HCV genotype 3 raise the question of whether 24 weeks or longer of therapy may be necessary to assure maximum SVR rates. This may be especially true in subjects with high baseline HCV RNA viral loads. The Genotype 3 Extended Treatment for Hepatitis C (GET-C) Study is designed to determine the efficacy of 24 or 48 weeks of therapy with PEG-IFN-alpha-2b plus RBV in patients infected with HCV genotype 3 and high baseline viral loads (ClinicalTrials.gov identifier NCT00255034).

Health-Related Quality-of-Life and Cost-Effectiveness Analysis of Peginterferon-Alpha with or Without Ribavirin

Current treatment regimens for the management of chronic HCV infection can affect quality of life and are costly. Rasenack and colleagues (2003) have compared the effect of monotherapy with PEG-IFN-alpha-2a or unmodified interferon on the health-related quality of life in treatment-naïve subjects with chronic HCV infection. The Fatigue Severity Scale (FSS), including the visual analogue scale (VAS), was used to measure fatigue severity. Health-related quality of life measures were assessed using the Short-Form health survey (SF-36). Therapy duration in both groups was 48 weeks. The PEG-IFN-alpha-2a patients had better mean FSS total scores and FSS VAS scores during the first 24 weeks and at week 48, respectively, when compared with subjects receiving unmodified interferon. The SF-36 domain scores were better at week 12 but not at week 24 or 48 in patients in the PEG-IFN-alpha-2a versus the unmodified interferon group. Overall, subjects receiving PEG-IFN-alpha-2a reported less fatigue and less body pain and performed better on a daily basis than patients receiving unmodified interferon. The mean FSS and SF-36 scores were improved in patients who achieved an SVR versus those subjects who did not experience an SVR.

The question as to whether monotherapy with PEG-IFN-alpha is cost-beneficial has been studied in a cost-benefit analysis of treatment-naïve subjects with chronic HCV infection. Outcome data were reviewed from published studies of PEG-IFN-alpha monotherapy (Shepherd et al., 2004). The authors concluded that the use of peginterferon-alpha was overall cost-effective, with an increase in this benefit in subjects infected with genotypes 2 and 3.

Hassanein (2004) performed a health-related quality-of-life analysis utilizing data from a large multinational study of patients with chronic HCV infection. Patients were treated with PEG-IFN-alpha-2a with or without RBV or unmodified interferon-alpha-2b plus RBV. The Fatigue Severity Scale (FSS) and the SF-36 Health Survey were used to assess the effect of therapy on health-related quality of life. Patients receiving PEG-IFN-alpha-2a plus placebo fared better on health-related quality-of-life measures (SF-36 and FSS) versus subjects in the PEG-IFN-alpha-2a/RBV and unmodified interferon/RBV groups. Patients receiving PEG-IFN-alpha-2a/RBV reported better health-related quality-of-life measures on both SF-36 and FSS surveys over the 48 weeks of therapy than those receiving unmodified interferon/RBV. Significant differences were reported in vitality, social functioning, body pain, and total fatigue and fatigue severity. Improvements in health-related quality-of-life scores in favor of the PEG-IFN/RBV group were observed as early as week 2 of therapy. Patients who achieved an SVR had improved quality of life, with the greatest improvement over baseline in role-emotional, vitality, general health, and role limitation physical domains in the SF-36 survey. Fatigue severity decreased significantly in subjects experiencing an SVR versus those who did not. Studies investigating the cost-effectiveness of treatment of chronic HCV infection utilizing PEG-IFN-alpha-2b/RBV compared with unmodified interferon/RBV have been published (Bernfort et al., 2006; Buti et al., 2005; Siebert et al., 2003).

Although the studies varied in design, the PEG-IFN-alpha-2b/RBV regimens were cost-effective when compared with unmodified interferon/RBV regimens in the Swedish, Spanish, and German healthcare systems.

Sullivan (2006) analyzed the cost-effectiveness of the combination of PEG-IFN-alpha-2a/RBV compared with unmodified interferon-alpha-2b/RBV. The authors concluded that the combination of PEG-IFN-alpha-2a plus RBV prolongs life expectancy and saves medical costs when compared with unmodified interferon-alpha-2b with RBV in the U.S. healthcare system. Hornberger (2005) reported similar findings with PEG-IFN-alpha-2a/RBV compared with no therapy in subjects with mild chronic HCV infection. The authors utilized United Kingdom treatment patterns in the design of their study.

Improvement in the quality of life, especially early in therapy, with PEG-IFN with or without RBV may reduce the need to alter doses based on subjective findings, encourage patients to complete the duration of therapy, and increase the likelihood of achieving an SVR. Therapy of chronic HCV infection with PEG-IFN with or without RBV is cost-effective when compared with unmodified interferon therapy in a variety of healthcare systems.

Special Patient Populations

Acute HCV Infection

Another avenue to decrease the impact of prolonged HCV infection and its complications is to treat patients upon presentation with acute HCV infection. Acute HCV infection may be difficult to identify and is often asymptomatic. Infection is acquired through intravenous drug abuse, needle-stick injury in healthcare workers, medical procedures utilizing inappropriately sterilized equipment, and sexual activity. Spontaneous viral clearance may occur in 14–46% of patients and may occur within 8 to 14 weeks of the onset of disease (Seeff, 2002; Kamal et al., 2006). The optimal timing to initiate therapy and the length of treatment have not been definitively determined. Kamal and colleagues (2006, 2006a) have investigated these two issues in randomized controlled clinical trials. In the first study, Kamal (2006) enrolled 129 patients with acute HCV infection to determine the optimal time to initiate therapy. Patients were divided into three groups and therapy was begun 8 weeks, 12 weeks, and 20 weeks after onset of disease. Patients in each group received PEG-IFN-alpha-2b (1.5 µg/kg/week) for a total of 12 weeks. Patients who did not want therapy were followed as a control group. Approximately 30% of subjects in the control group had a spontaneous clearance of HCV. The overall SVR was 88%. The SVR rates for the weeks of initiation of therapy were 95% (week 8), 93% (week 12), and 76% (week 20). The overall SVR rates by genotype were 72% (genotype 1), 100% (genotype 2), 93% (genotype 3), and 84% (genotype 4). Predictors of an SVR were non-1 genotype and a low baseline HCV RNA viral load. Kamal (2006a) performed a study to determine the optimal duration of therapy for the management

of acute HCV infection. Patients were randomized to receive 8 weeks, 12 weeks, or 24 weeks of therapy. Participants received the same dose of peginterferon-alpha-2b listed above. The overall SVR rate was 80% with 68%, 82%, and 91% of patients achieving an SVR after 8, 12, and 24 weeks of therapy, respectively. As a result of these two studies, the authors made the following recommendations for the treatment of patients with acute HCV infection. Patients infected with HCV genotype 1 (especially with a high baseline viral load) should begin therapy at 8 weeks after infection and continue for 24 weeks. Subjects infected with genotype 2 or 3 should begin therapy at 12 weeks after infection and continue therapy for 8 to 12 weeks. They made the caveat that the number of patients in the study infected with genotype 2 or 3 was small, however. Patients infected with genotype 4 should begin therapy at 12 weeks' post-infection and be treated for 12 weeks. Eight weeks of therapy may be an option in patients infected with HCV genotype 4 with low baseline viral loads. To avoid unnecessary treatment, initiation of therapy is delayed to account for the possibility of spontaneous viral clearance. More studies will be necessary to validate these suggestions.

African American Patients

African Americans (AA) appear to have a decreased response to interferon therapy with or without RBV for chronic HCV infection as compared with Caucasians (CA). Conjeevaram (2006) conducted a trial comparing the efficacy of PEG-IFN-alpha-2a (180 µg/week)/RBV (1–1.2 g/day) in AA versus CA who were treated for 48 weeks with a 24-week followup. Both groups were infected with HCV genotype 1. A difference between the two groups in virological response was evident from week 4 until week 48. Significantly more CA had undetectable HCV RNA serum levels than AA at all time points. The SVR rate was 28% and 52% in the AA and CA groups, respectively ($P < 0.0001$). The proportion of subjects that completed 80% of the maximum doses of both drugs differed significantly (54% AA and 73% CA, $P < 0.0001$). In addition, the AA patients had a higher mean body mass index, higher incidence of hypertension and diabetes, and lower neutrophil and hemoglobin levels than the CA patients. These factors may decrease response to therapy or tolerance of adverse effects of treatment regimens with PEG-IFN and RBV. In spite of these facts, the authors concluded that the amount of therapy completed, baseline viral loads, or disease characteristics did not explain the study findings. In a smaller study utilizing the identical medication regimen as above, Jeffers (2004) reported an SVR rate of 26% in the AA group and 39% in the CA group. The lower-than-expected response in the CA group was attributed to the small number in the study arm, the high drop-out rate, and the fact that fewer subjects were available for followup.

Jacobson (2004) compared the value of PEG-IFN-alpha-2b (1.5 µg/kg/week) with either weight-based (WB) (800–1,400 mg/day) or standard (SD) RBV doses (800 mg/day) in AA infected with HCV genotype 1. The SVR rates in the two dosing groups were 21% (WB) and 10% (SD). Dose reductions of RBV for anemia

were higher in the WB (12%) versus the SD (8%) group, but therapy discontinuation for adverse events was comparable between the two groups.

The Virahep-C trial is attempting to determine the etiology for the lower response rates to PEG-IFN/RBV regimens in AA versus CA. Howell (2006) noted that the poor virological response in AA could not be explained by altered pharmacokinetics or pharmacodynamics of PEG-IFN-alpha-2a during the first 4 weeks of therapy. Rhodes (2006) investigated the effect of the major histocompatibility complex on the likelihood of achieving an SVR in AA and CA patients. They reported that the HLA alleles A*02, B*58, and DPB*1701 are associated with an SVR. However, these alleles do not explain the observed difference in SVR rates between AA and CA. Su (2006) studied whether differences in interferon signaling could explain the observed SVR differences between AA and CA. The single nucleotide polymorphism rs3213545 in the OASL gene ("T" allele) was associated with SVR in both AA and CA. The "T" allele was found in approximately 51% and 31% of CA and AA, respectively. An SVR rate of 50.7% was observed in subjects with the "T" allele and 34.1% of participants without the allele. Burton (2006) looked at whether baseline HCV-specific immune responses could account for the difference in PEG-IFN/RBV-induced SVR between AA and CA. They measured the response of peripheral blood mononuclear cells to HCV antigens (core, E2, NS3, NS4, and NS5) of 179 AA and 174 CA. Approximately 31% of AA who had a combined baseline HCV antigen response at or above a specific threshold experienced an SVR versus only 23% with a lesser response. Similarly, 53% of CA who achieved the threshold response achieved an SVR versus 39% with a lesser response. In AA patients, 30.6% who achieved the threshold response achieved an SVR versus 22.5% with a lesser response. The authors conclude that regardless of race, baseline HCV-directed immunity is important to achieve an SVR. These results indicate that a definitive cause of the observed lower SVR rates in AA versus CA receiving PEG-IFN-alpha/RBV therapy remains elusive. The reduced response to pegylated interferons/RBV therapy in AA versus CA may result from a combination of negative predictive factors present in the AA population rather than a single etiology.

Persistently Normal Alanine Transaminase (PNALT) Levels

Persistently normal ALT (PNALT) levels in patients with chronic HCV infection may be present in up to 30% of subjects with chronic HCV infection (National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C, 2002). Shiffman (2006) reported that patients with PNALT levels have lower HCV RNA titers and lower liver inflammation and fibrosis scores on biopsy than patients with persistently elevated ALT levels. Approximately two-thirds of patients had portal fibrosis, and 10% revealed bridging fibrosis on liver biopsy. Quality of life is similarly impaired in subjects with PNALT as in HCV-infected patients with elevated ALT concentrations (Gane et al., 2005). These data indicate that patients with PNALT levels and chronic HCV infection should be considered for therapy since ALT concentrations do not correlate with liver pathology and patients

are at risk for disease progression. Zeuzem (2004a) reported the results of an international, multicenter, randomized trial of the efficacy of PEG-IFN-alpha-2a (180 µg/week) plus RBV (800 mg daily) in chronic HCV-infected patients with PNALT levels. Patients were treated for 24 weeks (Group A) or 48 weeks (Group B). Patients with cirrhosis, other liver diseases, or co-infection with the human immunodeficiency virus (HIV) were excluded. An SVR was achieved in 30% (Group A) and 52% (Group B) of patients ($P < 0.001$). For HCV genotype 1 infected patients, an SVR occurred in 13% (Group A) and 40% (Group B) ($P < 0.001$). Patients infected with genotype 2 or 3 achieved an SVR 72% (Group A) and 78% (Group B) of the time ($P = 0.45$). Thirteen percent and 56% of subjects infected with HCV genotype 4 achieved an SVR in Group A and B, respectively. Treatment duration (48 weeks) and low baseline HCV load correlated with the likelihood of achieving an SVR in patients with genotype 1 or 4 but not for patients infected with genotype 2 or 3. Patients younger than 40 years of age had a higher chance of achieving an SVR than subjects over 40 years of age. Arora (2006) assessed the effect of achieving an SVR on overall quality-of-life measures in subjects with chronic HCV infection and PNALT. Patients who experienced an SVR had improved quality of life and lower fatigue than patients who did not respond to therapy.

Zehnter (2006) compared the value of PEG-IFN-alpha-2a (180 µg/week) combined with RBV (1–1.2 g/day) in 911 patients infected with HCV genotype 1 and elevated ALT concentrations and 265 subjects with PNALT levels. Patients received therapy for 48 weeks with a 24-week followup off therapy. Patient groups were well matched; however, subjects with PNALT levels tended to be younger. The SVR rates were 74% and 51% in subjects with PNALT levels versus those with elevated ALT concentrations, respectively. The authors surmised that the higher SVR in the patients with PNALT levels could be attributed to the younger age in this group. Overall, patients with PNALT concentrations should be considered for treatment based on factors similar to those in patients with elevated ALT levels. Therapy choices appear to be the same as in patients with chronic HCV infection and elevated ALT concentrations.

Nonresponders and Relapsers to Unmodified Interferon with or Without Ribavirin

Patients who do not achieve an SVR to interferon with or without RBV are designated as nonresponders. Null responders are nonresponders who fail to achieve less than a 2 log₁₀ decline in HCV RNA concentrations from baseline 12 weeks after therapy initiation. These patients rarely respond to additional therapy, and the most appropriate therapy for these patients is best determined in controlled trials (DiBisceglie et al., 2006). Evidence from Tang (2005) that rapid clearance of HCV may be important in enhancing host response to the virus may provide clues to the design of new treatment combinations for these difficult-to-treat patients. Although patients who relapse are not technically nonresponders, they will be discussed here.

The lead-in component of the HALT-C trial is investigating the value of retreatment of patients with chronic HCV infection and advanced fibrosis or cirrhosis who failed therapy with unmodified interferon with or without ribavirin (Shiffman et al., 2004). Subjects received PEG-IFN-alpha-2a at 180 µg/week with RBV (1–1.2 g/day). Patients with undetectable HCV RNA levels at week 20 were treated for a total of 48 weeks and followed for SVR at 24 weeks' post-therapy. Patients with detectable HCV RNA concentrations at 20 weeks were entered into the maintenance phase of the study. Although 32% of subjects were HCV RNA negative at week 48, the relapse rate was high and only 18% achieved an SVR. Factors associated with an SVR were absence of cirrhosis, prior treatment with interferon monotherapy, genotype 2 or 3, HCV RNA concentrations <1.5 million IU/mL, and an AST:ALT ratio <1.0.

Diago (2006) performed an induction dose study with PEG-IFN-alpha-2a plus RBV in HCV genotype 1 infected patients who had not responded to ≥22 weeks of unmodified interferon/RBV. No patients had cirrhosis. Patients were randomized to 180 µg/week, 270 µg/week, or 360 µg/week of PEG-IFN-alpha-2a with RBV (1–1.2 g/day) for 12 weeks followed by PEG-IFN at 180 µg/week with the same RBV dose for an additional 36 weeks. An SVR was achieved in 18% (180 µg/week), 30% (270 µg/week), and 38% (360 µg/week) in the respective dosing regimen arms. Izumi (2006) investigated the effect of PEG-IFN-alpha-2a (180 µg/week) plus RBV (600–1,000 mg/day) in Japanese patients with chronic HCV infection who had not responded to prior unmodified interferon monotherapy. A much higher rate of SVR was noted in this population than was found in the HALT-C trial or by Diago (2006). Forty-eight percent of patients had an SVR overall, and 50% of subjects infected with HCV genotype 1b experienced an SVR after 48 weeks of therapy.

Similar retreatment studies in subjects who did not respond to unmodified interferon with or without RBV have been performed by Taliani (2006), Jacobson (2005a), and Poynard (2005) utilizing PEG-IFN-alpha-2b with RBV. Although study population, trial design, and dosing regimens were different, the SVR rates are similar to those found with PEG-IFN-alpha-2a (180 µg/week/RBV) (15–21%). Gaglio (2005) found that fixed-dose RBV was equally as effective as weight-based dosing in patients who failed prior unmodified interferon-based therapy. Jacobson (2005a) noted an SVR of only 8% in subjects who were nonresponders to unmodified interferon/RBV therapy versus an SVR rate of 21% in subjects with no response to unmodified interferon monotherapy. Factors associated with an SVR in these studies were low baseline HCV RNA levels, low γ-glutamyltransferase (γ-GT), weight >75 kg, genotype non-1, and nonresponse to interferon monotherapy.

The "RENEW" study was designed to compare the benefits of 1.5 µg/kg/week versus 3.0 µg/kg/week of PEG-IFN-alpha-2b with RBV (800–1,400 mg daily) in the management of patients who had failed previous HCV therapy with unmodified interferon/RBV (Gross et al., 2005). Ninety-one percent of subjects had HCV genotype 1, 40% had a Metavir score 3 or 4 (F3/4), and 16% were African American (AA). Treatment duration was 48 weeks with a 24-week followup. An SVR occurred in 12% and 17% in the 1.5- and the 3.0-µg/kg/week dosing groups, respectively ($P = 0.03$). Overall, patients with F3/4 and African Americans had lower SVR rates; however, subjects in these groups receiving the higher dose of

PEG-IFN achieved comparable SVR rates to the other study members. The SVR rate for the 1.5- and 3.0- $\mu\text{g}/\text{kg}/\text{week}$ PEG-IFN-alpha-2b dosing regimens for AA subjects were 2.0% and 14%, respectively (Gross et al., 2005a). Therapy discontinuations and dose changes were comparable between the two dosing groups. Despite differences in study design, patient population, and dosing, the SVR rates with both PEG-IFN products in nonresponders to unmodified interferon-based regimens were remarkably similar (15–21%). Induction dosing with PEG-IFN-alpha-2a appeared to improve the chance of achieving an SVR, but further studies with larger numbers of patients will be necessary to validate these findings.

The likelihood of achieving an SVR is greater in patients who relapse after unmodified interferon monotherapy or combination therapy with RBV. Relapse is defined as a detectable HCV RNA in serum after a patient has had an end-of-therapy response (undetectable HCV RNA). Yoshida (2005) conducted a study including 119 patients who had relapsed after interferon monotherapy or combination therapy with RBV. Patients were assigned to receive either 24 or 48 weeks of PEG-IFN 180 $\mu\text{g}/\text{week}$ with 800 mg/day of RBV. Forty-seven percent of patients had advanced fibrosis. Overall, the SVR was 40%. Thirty-five percent and 51% of patients with genotype 1/2 or 3 experienced an SVR, respectively. Nevens (2005) found an overall SVR of 43% in subjects receiving 180 $\mu\text{g}/\text{week}$ of PEG-IFN-alpha-2a and RBV (1–1.2 g/day). Patients had relapsed after receiving unmodified interferon with or without RBV.

In the EPIC trial reported by Poynard (2005), patients who relapsed after therapy with unmodified interferon with RBV were treated for 48 weeks with 1.5 $\mu\text{g}/\text{kg}/\text{week}$ of PEG-IFN-alpha-2b with weight-based RBV. Nonresponders to this therapy were placed into the maintenance phase of the study. An overall SVR of 39% was achieved in relapse patients. The SVR rate was higher in the patients infected with HCV genotype 2 or 3 than in those with genotype 1 (58% vs. 29%). Similarly, Jacobson (2005a) reported an overall SVR of 42% in subjects who had relapsed after combination interferon/ribavirin therapy. Even though the medication regimens and patient populations were different, the overall SVR for patients who relapsed after unmodified interferon with or without ribavirin were comparable between the two peginterferons.

Herrine (2005) investigated the value of combining PEG-IFN-alpha-2a 180 $\mu\text{g}/\text{week}$ with or without RBV with amantadine (AMD) or mycophenolate mofetil (MMF) in patients who had an increase in HCV RNA levels during therapy (break-through) or relapse during or after receiving unmodified interferon/RBV therapy. Subjects were assigned to one of four treatment groups. Group A received PEG-IFN-alpha-2a plus RBV (800–1,000 mg daily), Group B received PEG-IFN-alpha-2a plus 1 g of MMF orally twice daily, Group C received PEG-IFN-alpha-2a and AMD 200 mg daily, and Group D received PEG-IFN-alpha-2a plus AMD 200 mg daily plus ribavirin (800–1,000 mg daily). Treatment duration was 48 weeks with a 24-week followup period. An SVR was achieved in 37.5 % (Group A), 17.2% (Group B), 9.7% (Group C), and 45.2% (Group D) of subjects. Only Groups D and C were significantly different when compared, $P = 0.02$. The study revealed no clear advantage of combining amantadine to PEG-IFN/RBV therapy. The combination of AMD with MMF and PEG-IFN alone offered no advantage over RBV-containing

regimens. More study will be necessary with combination therapy (Group A versus Group D) plus standard doses of ribavirin (1–1.2 g/day) to determine efficacy in relapse or breakthrough situations.

The ideal therapy with which to treat patients who do not respond or relapse after therapy with unmodified interferon/ribavirin regimens has not been definitively determined. It is known, however, that the risk of a nonresponse or relapse is increased in subjects who require dosage reduction of PEG-IFN and RBV during therapy (Ferenci et al., 2005; Shiffman et al., 2004). Steps to reduce the need for regimen alterations, including supportive medications (i.e., erythropoietin, filgrastim) and psychiatric evaluation, should be considered as part of any retreatment with PEG-IFN/RBV (Collantes & Younossi, 2005). An assessment of adherence is also important, and adherence-building exercises should be considered. Treatment of alcohol and other substance abuse conditions is critical before beginning retreatment.

Relapse or Nonresponse to Peginterferons

Few studies have looked at treatment of patients who have failed therapy with PEG-IFN-alpha/RBV. Berg (2006a) took patients who relapsed after 24 weeks of PEG-IFN-alpha-2a at 180 µg/week with RBV (800 mg or 1–1.2 g daily) and retreated them for an additional 48 weeks. Treatment was initiated at the same dose (PEG-IFN-alpha-2a/ribavirin) they had received before. The overall SVR was 55%. Fifty-one percent and 64% of subjects infected with HCV genotypes 1 and 2 or 3 achieved an SVR, respectively. Kaiser (2006) compared the efficacy of consensus interferon/RBV with PEG-IFN-alpha-2a/RBV in subjects who had relapsed after 48 weeks of PEG-IFN/ribavirin therapy. Group A received daily consensus interferon (9 µg), and Group B received standard PEG-IFN (180 µg/week) dosing. Both groups received weight-based RBV for a total of 72 weeks. Eighty-three percent of patients were infected with HCV genotype 1. The SVR for Groups A and B were 69% and 44%, respectively, $P < 0.05$. A clinical study is under way to determine the safety and efficacy of daily high-dose consensus interferon/RBV therapy in subjects who are nonresponders to combined PEG-IFN-alpha and ribavirin (ClinicalTrials.gov identifier: NCT00266318).

The “REPEAT” study is a multinational trial to test the value of an induction dose of PEG-IFN-alpha-2a plus RBV compared with standard-dose PEG-IFN-alpha-2a/RBV in patients who are nonresponders to PEG-IFN-alpha-2b/RBV therapy. Patients were randomized to four treatment groups. Groups A and B received PEG-IFN-alpha-2a at 360 µg/week for the first 12 weeks followed by 180 µg/week for a total of either 72 or 48 weeks, respectively. Groups C and D received PEG-IFN-alpha-2a at 180 µg/week for a total of either 72 or 48 weeks, respectively (Marcellin & Jensen, 2005). All groups received RBV (1–1.2 g/day). The results of the first 12 weeks of the trial have been presented. The high-dose induction groups of the study appear to be more effective in lowering HCV RNA concentrations than the standard PEG-IFN dosing arms. Forty-three percent of subjects in Groups A and B

had undetectable HCV RNA concentrations at 12 weeks of therapy versus 26% in Groups C and D. Whether these results will translate into an improved SVR awaits completion of the study.

Role of Maintenance Therapy in Patients Who Fail to Respond to Interferon-Based Therapy

The HALT-C, EPIC, and COPILOT trials are three randomized controlled studies whose goal is to determine whether maintenance therapy with PEG-IFN- α will decrease the progression of disease in subjects with chronic HCV infection and advance disease compared with no therapy or placebo (Shiffman et al., 2004; Poynard et al., 2005; Curry et al., 2005). Patients had failed prior unmodified interferon/RBV therapy. Whether maintenance therapy will be of value in preventing disease progression awaits the final results of these studies.

Experimental Therapy

It is clear that we have gone about as far as we can go with PEG-IFN/RBV therapy for patients with chronic HCV infection. New modalities that attack the hepatitis C virus at different sites are under development. The serine protease inhibitors are being investigated for their ability to inhibit hepatitis C viral replication. Agents under development include VX-950 and SCH 503034 (Reesink et al., 2005; Zeuzem et al., 2006a). Reesink (2005) performed a phase 1B trial with VX-950 in healthy adults and patients infected with HCV genotype 1. Patients assigned to the 750-mg q8h group experienced the greatest decrease in HCV RNA concentrations after 14 days of treatment (median drop of 4.4 \log_{10}). The NS3 protease inhibitor (SCH 503034) was administered to HCV genotype-infected patients who had failed therapy with PEG-IFN- α -2b with or without RBV. Patients received varying doses of SCH 503034 alone or with PEG-IFN- α -2b for a period of 14 days using a three-way crossover design. A 2- to 3-week washout period occurred between each dosing regimen. Interestingly, undetectable HCV RNA concentrations were found in 4 of 10 patients after 14 days of PEG-IFN plus 400 mg of SCH 503034. These inhibitors will need to be used in combination with other HCV-active antiviral agents due to the emergence of resistant serine protease if used alone (Lin et al., 2006, Zeuzem et al., 2006). Combination phase II studies with PEG-IFN- α -2a and 2b are under way (ClinicalTrials.gov Identifier NCT00336479; ClinicalTrials.gov Identifier NCT00160251).

Valpovicitabine (NM283) is a viral RNA polymerase inhibitor that is under study in HCV treatment-naïve and nonresponders to prior interferon-based therapies (Pockros et al., 2006; Dieterich et al., 2006). Pockros (2006) outlined the 24-week effects on HCV RNA baseline concentrations of valpovicitabine alone, in combination with PEG-IFN- α -2a compared with PEG-IFN- α -2a/RBV. Patients were infected with HCV genotype 1 and were nonresponders to PEG-IFN/RBV therapy. Subjects were randomly assigned to five treatment groups, including PEG-IFN- α -2a at

180 µg/week plus RBV (1–1.2 g/day) (A), PEG-IFN-alpha-2a at 180 µg/week and various doses of valopicitabine (B–D), or valopicitabine monotherapy (E). Subjects in the 800-mg/day valopicitabine/PEG-IFN-alpha-2a group had a greater mean decline of HCV RNA (3.32 log₁₀ IU/mL) versus PEG-IFN-alpha-2a/RBV or valopicitabine monotherapy, 2.31 log₁₀ IU/mL and 0.54 log₁₀ IU/mL, respectively. Dieterich (2006) administered valopicitabine/PEG-IFN-alpha-2a to treatment-naïve HCV genotype 1 infected patients and reported a mean decrease of 4.5 log₁₀ IU/mL in subjects after 8 weeks of combination therapy.

A Toll-like receptor 9 agonist (CPG 10101-CPG) is being investigated in phase II studies. The drug acts by stimulating the immune system. McHutchison (2006) has reported on the first 12 weeks of CPG monotherapy, CPG in combination therapy with PEG-IFN-alpha-2b with or without RBV or with RBV alone, compared with PEG-IFN-alpha-2b plus RBV. Subjects were infected with HCV genotype 1 and had relapsed after PEG-IFN /RBV therapy. At 12 weeks, 57% and 86% of patients receiving PEG-IFN/RBV or PEG-IFN/RBV plus CPG had achieved an EVR, respectively ($P = 0.21$).

Interest in improving the tolerability of PEG-IFN/RBV therapy has led to the development of the drug viramidine. Viramidine is a pro-drug of RBV that is being investigated for use with interferon due to its lower incidence of anemia. Benhamou (2006) reported on the results of a phase III study comparing PEG-IFN-alpha-2b combined with weight-based RBV (1–1.2 g/day) or viramidine (V) (600 mg twice daily). An SVR was achieved in 52% (RBV) and 38% (V) of patients in each group (intent-to-treat) and did not meet the non-inferiority efficacy endpoint. Anemia was found in 24% and 5% of subjects in the RBV and V groups, respectively. The authors noted an increase in SVR with increasing mg/kg dose of V. Anemia was not increased proportionally. Revision of the standard dose of viramidine is likely to result from this study.

A variety of other agents are under investigation for the management of treatment-naïve or nonresponders/relapsers to interferon-based therapies. Most of the agents discussed here are in phase II or early phase III studies, and whether they will have a role in the management of HCV-infected individuals will be determined by results from controlled studies. Due to concerns about viral resistance when these agents are used alone, combination regimens including PEG-IFN will likely be necessary.

Children

The management of chronic HCV-infected children and adolescents with PEG-IFN-based therapy has not been extensively studied. A trial by González-Peralta (2005) recorded an overall SVR rate of 46% (54/118) in children treated for 48 weeks with unmodified interferon/RBV. An SVR was realized in 36% and 84% of children infected with HCV genotypes 1/2 or 3, respectively. Interestingly, Schwarz (2003) reported an SVR of 38% (5/13) children receiving PEG-IFN-alpha-2a (180 µg/1.73 m² × patient's body surface area) monotherapy for 48 weeks. Ninety-two percent (12/13) of patients were infected by HCV genotype 1. Wirth (2005) treated

62 children and adolescents with chronic HCV infection with PEG-IFN-alpha-2b (1.5 µg/kg/week)/RBV (15 mg/kg daily). Subjects infected with HCV genotype 1 were treated for 48 weeks, while patients with HCV genotype 2 or 3 were given the option of receiving 24 weeks of therapy. The overall SVR was 56%. The SVR rate in patients with HCV genotypes 1 and 2 or 3 were 48% and 100%, respectively. Utilizing the same dosing regimen as Wirth (2005), Hasan (2006) found an SVR rate of 75% (9/12) in a small group of adolescents infected with HCV genotype 4. Although these studies do not show the superiority of PEG-IFN/RBV regimens over unmodified interferon/ribavirin treatments, the once-weekly dosing of the peginterferon may appeal to busy parents/children.

Liver Transplantation

Use of PEG-IFN therapy in the post-liver transplant population is an evolving practice with new clinical information being published at a rapid pace. As more liver transplantation programs emerge and grow, and more high-risk transplants are performed, recurrent hepatitis C in the recipients will likely rise, with the potential for graft loss (Lauer & Walker, 2001; National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C, 2002). High doses of immunosuppressive agents immediately post-transplantation present a particular problem in terms of tolerability of treatment with PEG-IFN and RBV. For this reason, treatment is recommended to be held until months after transplantation, with two scenarios being explored most often. The first is the use of PEG-IFN as preemptive or “prophylactic” treatment before clinical onset of recurrent hepatitis C, relatively early (e.g., one month) post-transplant in high-risk patients with high viral loads. The second is the use of PEG-IFN for treatment of recurrent hepatitis C, later post-transplant (e.g., six months). Much of the literature describing this use has been published for unmodified interferon therapies (Singh et al., 1998; Sheiner et al., 1998; Firpi et al., 2002; Berenguer Prieto et al., 2004; Giostra et al., 2004; Bizollon et al., 2003). Although interferon-based therapies carry theoretical risks of inducing graft rejection, recent trials do not support the association (Kuo & Terrault, 2006; Chalasani et al., 2005).

In a study of the two treatment scenarios mentioned above, preemptive treatment and active therapy of recurrent hepatitis C in patients following liver transplantation, Chalasani et al. (2005) enrolled 54 patients within 3 weeks of an orthotopic liver transplantation (OLT) for “prophylaxis” or preemptive therapy and enrolled 67 patients 6 to 60 months after transplantation for active treatment of recurrent HCV disease. In either treatment group, patients were randomized to treatment with 180 µg/week of PEG-IFN-alpha-2a or no antiviral treatment for 48 weeks with a 24-week followup post-therapy. In the preemptive arm, patients who received PEG-IFN had a significantly greater drop in HCV RNA concentrations at weeks 4 and 24 than untreated patients ($P < 0.003$ and $P < 0.02$, respectively). Likewise, patients in the treatment arm on PEG-IFN-alpha-2a had significantly lower viral loads than untreated patients at each scheduled post-baseline assessment ($P < 0.001$). Unfortunately, only 2 treated patients in the prophylaxis trial (8%) and 3 in the

treatment trial (12%) achieved an SVR. Acute rejection rates were similar in the treated and untreated groups in both the prophylaxis (12% vs. 21%; $P < 0.5$) and treatment (12% vs. 0%; $P < 0.1$) trials.

A preemptive-only, randomized comparative study of single therapy or combination therapy with RBV of unmodified interferon-alpha-2b 3 MU three times a week versus PEG-IFN-alpha-2b 1.5 $\mu\text{g}/\text{kg}$ once weekly was conducted by Shergill (2005). Therapy was initiated two to six weeks' post-transplantation and continued for 48 weeks. Fifty-one patients were treated, but with a high rate of dose reductions (85%) and drug discontinuations (37%) due to adverse events and intolerability. Rates of viral suppression at 48 weeks (ETR) were low for both groups, 4.5% for single therapy with either interferon product versus 22.7% for combination therapy with either product ($P = 0.093$). The difference was not statistically significant due to the low total number of patients. Even lower comparative rates were recorded for SVR at 4.5% for monotherapy and 18.2% for combination therapy. Comparisons could not be performed regarding unmodified versus PEG-IFN products due to the small number of patients. The authors concluded that while combination therapy was better than monotherapy, SVR rates are far less than in non-transplantation HCV-infected patients, and a majority of patients did not tolerate the drug therapy well. In a post hoc analysis, the authors concluded that the best candidates for treatment are patients with better liver function (MELD score) prior to treatment and those who undergo living donor transplantation.

A French study investigated the benefit of active treatment of recurrent HCV disease post-liver transplantation. Dumortier (2004) treated 20 patients with 12 months of combination therapy with PEG-IFN-alpha-2b and RBV. They evaluated virological and biochemical responses to treatment. Patients were started on low-dose treatment at 0.5 $\mu\text{g}/\text{kg}/\text{week}$ of PEG-IFN plus 400 mg of RBV daily. Therapy was initiated at least 28 months' post-transplantation, and dosing was escalated as tolerated to a maximum dose of PEG-IFN of 1 $\mu\text{g}/\text{kg}/\text{week}$ and 1,200 mg of RBV daily. A high rate of adverse events, at 20%, led to drug discontinuation. Dose reductions of PEG-IFN to 0.5 $\mu\text{g}/\text{kg}/\text{week}$ were required in 37.5% of the remaining patients, and dose reductions of RBV were required in 87% of the remaining patients. Using intent to treat, 55% of the patients had a virological response at 12 months, with an SVR of 45%. Like most studies, virological outcomes were less for genotype 1 than other genotypes (64% vs. 100%, respectively, $P < 0.05$). Five of the patients in this study had a mild acute rejection episode.

Neff (2004) examined the benefits of treatment of recurrent HCV in liver transplant recipients using combination therapy with PEG-IFN-alpha-2b (1.5 $\mu\text{g}/\text{kg}/\text{wk}$) and RBV (400–600 mg/day) therapy for at least 48 weeks. The retrospective review identified 57 patients, who were divided into patients who were treatment-naïve versus those who had received interferon-based therapy pre-transplant and were nonresponders to at least six months of combination therapy. Undetectable HCV RNA concentrations were attained in eight (27.6%) treatment-naïve patients and six (21%) treatment-experienced patients at the end of 48 weeks of therapy. An SVR was achieved in 75% (6/8) and 33% (2/6) of treatment-naïve and treatment-experienced patients, respectively. Ribavirin or PEG-IFN dose reductions were required in both groups. Up to 69% of treatment-naïve patients had dose reductions.

A Spanish study conducted by Planas (2005) treated patients with evidence of recurrent HCV infection after liver transplantation with PEG-IFN-alpha-2b at 1.5 $\mu\text{g}/\text{kg}/\text{week}$ plus weight-based ribavirin (10.6 $\text{mg}/\text{kg}/\text{day}$). The 30 patients were treated at a median of 43 months' post-transplantation. Treatment duration was dependent upon HCV genotype, 48 weeks for genotypes 1 and 4 or 24 weeks for genotypes 2 and 3. An end-of-treatment response was measured at 63%, with an SVR measured at 47%. Dose reductions were required in 40% of patients.

Other small case series include open-label reviews of patients with recurrent HCV after liver transplantation by Biselli (2005), Beckebaum (2004), Mukerjee (2003), and Oton (2005). Patients were treated with combination therapy including PEG-IFN plus RBV. All four are observational studies designed to examine the benefits of combination therapy with PEG-IFN-alpha-2b plus RBV. In the study by Biselli (2005), the dose chosen for PEG-IFN-alpha-2b was 1.0 $\mu\text{g}/\text{kg}/\text{week}$ and RBV at 600 mg/day . Therapy was continued for at least six months. Nine patients (45%) had an end-of-treatment response, and an SVR was attained in 60% of treatment-naïve patients versus 30% of previously treated nonresponders. A drop-out rate of 45% was observed at six months. In the study by Beckebaum (2004), 12 patients were treated with 3 months of unmodified interferon, followed by 9 months of PEG-IFN-alpha-2b at 1.5 $\mu\text{g}/\text{kg}/\text{week}$ plus RBV (10–12 mg/kg). An ETR was observed in 33% of patients. A disappointing 42% had no response after six months of treatment. The study by Mukherjee (2003) followed 39 patients receiving PEG-IFN-alpha-2b at 1.5 $\mu\text{g}/\text{kg}/\text{week}$ and RBV at 800 mg/day . In this more standard dose study, 17 patients withdrew within the first three months due to drug intolerance. Four had not yet completed 3 months of treatment at the time of publication. Of the 18 patients who completed treatment, 17 (94.4%) or 43.6% of the total enrolled had an early virological response (HCV RNA undetectable at 3 months). An end-of treatment response (ETR) was achieved in 15 (83.3%) or 38.5% of the total enrolled patients at six months. An SVR occurred in 12 patients, with results pending for three other subjects. Oton (2005) reviewed outcomes in 21 treatment-naïve patients who received PEG-IFN-alpha-2b at 1.5 $\mu\text{g}/\text{kg}/\text{week}$ plus RBV at a weight-based dose of at least 10.6 $\text{mg}/\text{kg}/\text{day}$. The time from liver transplantation was at least 1.7 years. All patients were infected with HCV genotype 1. Treatment was intended for at least 48 weeks. Two patients dropped out, one due to intolerance, the other due to non-drug-related cholangitis. Necessary dose adjustments were high, at 14% for PEG-IFN and 32% for RBV. Fourteen patients (66.7%) had an ETR, with an SVR reported in 42.8% of patients, demonstrating one of the highest response rates among these observational studies.

Initial results of a randomized, multicenter study investigating the efficacy of PEG-IFN-alpha-2a in patients with recurrent HCV infection following liver transplantation were presented in abstract form (Vogel et al., 2002). The time of therapy initiation varied widely, within 6 to 60 months of liver transplantation. All patients were treatment-naïve. Patients were assigned to receive either PEG-IFN at 180 $\mu\text{g}/\text{week}$ or placebo. The majority of patients in both groups had a viral load >1 million IU/mL at baseline and HCV genotype 1. Treatment was continued for 48 weeks with a 24-week followup that was still pending. At 48 weeks of therapy, 35% of patients receiving active treatment with PEG-IFN and none of the patients receiving placebo had an undetectable HCV RNA level.

The published experience for preemptive therapy or treatment of recurrent HCV infection in liver transplant patients demonstrates fairly low success rates with a reasonably high amount of drug intolerance. Larger prospective dose-ranging studies would help define the ideal approach. In the meantime, initiation of therapy with PEG-IFN plus RBV at lower doses with titration upward as tolerated, and careful monitoring and support with growth factors, appear to be a reasonable approach. The pharmaco-economic benefit of PEG-IFN-based therapies in this patient population has yet to be defined.

Human Immunodeficiency Virus (HIV) Co-infection

In the United States and Europe, between 15% and 30% of all people infected with HIV are also infected with HCV (Sulkowski et al., 2000; Sherman et al., 2002; Greub et al., 2000; Sulkowski et al., 2002). Rates are higher in people who contract the disease through intravenous drug abuse (Garfein et al., 2000) than among men who contract the disease through sexual contact with other men. However, there have been spikes in the incidence in the population of men who have sex with men (MSM), likely linked to the resurgence of unprotected sex (Sulkowski & Thomas, 2003; Rauch et al., 2005; Ghosn et al., 2004). Co-infected patients often have lower CD4 counts, a more rapid progression of liver fibrosis, and increased mortality over people who are singly infected (Nunez et al., 2003; Brau, 2003; Kramer et al., 2005; Sulkowski et al., 2002; Tedaldi et al., 2003). Although there may be some disagreement among researchers, co-infection with HCV does not appear to affect progression or response to therapy of HIV disease (Sulkowski et al., 2002; Sullivan et al., 2006; Hershov et al., 2005).

Data are growing exponentially on the treatment and management of patients with HCV/HIV co-infection. The publication of two well-designed, large, randomized studies has expanded the level of evidence for treating co-infected patients (Table 4). The AIDS Pegsys RBV International Co-infection Trial (APRICOT) evaluated the efficacy and safety of unmodified interferon-alpha-2a (3 MU 3 times/week) plus RBV (800 mg/day) versus PEG-IFN-alpha-2a at 180 μ g/week plus placebo versus PEG-IFN plus RBV (800 mg/day) (Torriani et al., 2004). Patients were young, with a mean age of 40 years, mostly male, white and primarily infected with HCV genotype 1 (60%). Inclusion criteria were compensated liver disease, a CD4⁺ cell count \geq 100 cells/mL, and stable HIV disease (with or without HIV therapy). Sustained virological response rates were lower than for mono-infected patients, and the highest SVR response occurred in the group treated with PEG-IFN plus RBV (40%). However, the SVR rate for unmodified interferon plus RBV was only 12%. The SVR rate for patients receiving PEG-IFN plus placebo (20%) was also lower than the combination with RBV. Like mono-infection trials, patients infected with HCV genotype 1 were more treatment refractory. For these patients, the best chance for achieving an SVR was observed when subjects received the combination of PEG-IFN plus RBV (29% vs. 14% and 7%) versus the PEG-IFN plus placebo or unmodified interferon plus RBV groups, respectively.

Table 4 An Overview of Trial Design/Results for Treatment of HIV and HCV Co-infected Patients with Pegylated Interferon

Study Design	APRICOT (Torriani et.al. 2004)	PRESCO (Ramos 2006)	ACTG 5071 (Chung 2004)	RIBAVIC (Carrat 2004)
Sites Number of patients	International (19 countries) 868	Spain (1 site) 98	US (21 sites) 133	France(71 centers) 412
Outcome measures	Clinical/Safety	Clinical/Safety	Clinical/Safety	Clinical/Safety
Arm 1	PEG-IFN alpha-2a 180 mcg weekly + RBV 800/d	PEG-IFN alpha-2a 180 mcg weekly + RBV 800-1200 mg/d	PEG-IFN alpha-2a 180 mcg weekly + RBV 600 mg × 4wks then 800 mg × 4 wks then 1000 mg/d	PEG IFN alpha-2b 1.5 mcg/kg weekly + ribavirin 400 mg twice daily
Arm 2	PEG-IFN alpha-2a 180 mcg weekly + placebo	None	PEG-IFN alpha-2a 180 mcg weekly + placebo	IFN alpha-2b 3MU three times a week +ribavirin 400 mg twice daily
Arm 3	IFN alpha-2a 3MU three times weekly + RBV 800/d	None	IFN alpha-2a 6MU three times weekly × 12 weeks, then 3mu three times weekly + RBV 600 mg × 4wks then 800 mg × 4 wks then 1000 mg/d	None
Treatment duration (weeks)	48	12 (interim results)	48	48
RESULTS				
SVR genotype 1	PEG-IFN + RBV 29% + placebo 14%	NA	PEG IFN + RBV 14% + RBV 6%	PEG IFN + RBV 17% + RBV 6%
Overall SVR (week 72)	PEG-IFN + RBV 40% + placebo 20%	EVR: 83%	PEG IFN + RBV 27% + RBV 12%	PEG IFN + RBV 27% + RBV 20%

The RIBAVIC trial (Carrat et al., 2004), a multicenter, randomized, parallel group, open-label trial, examined the safety and efficacy of PEG-IFN-alpha-2b plus RBV versus unmodified interferon-alpha-2b plus RBV in HIV-HCV co-infected patients (Table 4). The study was conducted in 71 French centers. Dosing for PEG-IFN-alpha-2b was 1.5 µg/kg/week versus interferon-alpha-2b 3 MU three times a week, both arms with RBV at 800 mg/day. An SVR was attained at a higher rate for the PEG-IFN regimen than unmodified interferon (27% vs. 20%, = 0.047), respectively. Different rates of SVR were even more pronounced when comparing patients infected with genotype 1 who were assigned to PEG-IFN-alpha-2b versus unmodified interferon (17% vs. 6%, respectively, $P = 0.006$). When comparing SVR rates for genotypes 2 and 3, there was not a statistically significant difference in SVR rates between those treated with PEG-IFN product (44%) versus unmodified interferon (43%).

Another multicenter randomized trial by Chung (2004) evaluated the efficacy of unmodified interferon-alpha-2a or PEG-IFN-alpha-2a, both with escalating doses of RBV (600–1,000 mg/day) (Table 4). Patients treated with the PEG-IFN-alpha-2a/RBV regimen experienced a higher SVR rate versus unmodified interferon/RBV (27% and 12%). An SVR was achieved in only 6% (unmodified interferon group) and 14% (PEG-IFN group) of patients infected with HCV genotype 1, respectively.

The PRESCO trial (Ramos et al., 2006), in progress, examines the benefit of weight-based doses of ribavirin (1,000–1,200 mg/day) compared to the standard RBV dose (800 mg/day) utilized in the APRICOT trial (Table 4). Data up to week 12 have been presented in abstract form. For HCV genotype 1, an EVR (2 log₁₀ decrease in HCV RNA concentrations at 12 weeks of therapy) was observed in 78% of the study subjects. This compares to 63% in APRICOT and 80% of subjects in the HCV mono-infection trial (Fried et al., 2002). Differences were less pronounced in patients with genotypes 2 and 3. Whether these results will translate into a better SVR rate awaits the conclusion of the study.

Voight (2006) performed a prospective, uncontrolled, multicenter trial in Germany, exploring the efficacy and safety of combination PEG-IFN-alpha-2b (1.5 µg/kg/week) plus RBV (800 mg daily) for 48 weeks for HCV genotypes 1 and 4 and 24 weeks for genotypes 2 and 3 in HIV/HCV co-infected patients. An end-of-treatment response was found in 52% of patients overall, but an SVR response occurred in only 25% of subjects. This rate was lowest for those with genotype 1 or 4 (18%) and highest for genotype 2 or 3 (44%). Discontinuation rates were high (30%).

Soriano (2004) investigated whether an early virological response at 12 weeks (EVR- undetectable HCV RNA or ≥ 2 log₁₀ decrease of HCV RNA concentrations) could be used to make treatment decisions in HCV patients co-infected with HIV. Of the 89 co-infected patients, an EVR occurred in 58% of patients, and 32.6% attained an SVR. The negative and positive predictive value for achieving an SVR was 100% and 56%, respectively. From these results, consideration of treatment discontinuation can be entertained after 12 weeks of therapy if there is no EVR regardless of infecting HCV genotype in HCV/HIV co-infected patients receiving PEG-IFN-based therapies.

In a later investigation by the same group (Soriano, 2004a), high relapse rates were observed in up to 32.8% of treated patients who have an ETR. As a result, other groups have explored prolonged treatment durations for co-infected patients, despite undetectable HCV-RNA concentrations at the end of therapy. An Italian group examined the benefits of continuing treatment of co-infected patients with chronic HCV genotype 2/3, beyond 24 weeks, even if there was a treatment response to PEG-IEN plus RBV (Zanini et al., 2006). Unfortunately, many of the patients (36%) could not tolerate even 24 weeks of therapy due to adverse events. Those able to complete therapy up to 48 weeks had a lower relapse rate than those who could only complete 24 weeks of therapy (11% vs. 39%).

The benefits of treating acute hepatitis C in HIV-infected patients are still not well known. A German group is studying treatment with PEG-IFN plus RBV for acute HCV infection in patients with HIV (Vogel et al., 2006). The majority of patients were infected with genotype 1. The interim analysis was that, after 24 weeks of therapy with PEG-IFN-alpha-2a with or without RBV, 61% of patients had undetectable HCV RNA levels. No significant differences in these outcomes between HCV genotypes or with the addition of RBV were seen. Early virological responses at weeks 4 and 12 were the only significant predictors of this response. The discontinuation rate was low, 6% due to adverse events.

A French group (Dominguez et al., 2006) published results of a prospective pilot study of 25 patients with acute HCV infection (less than six months) treated with PEG-IFN-alpha-2a at 180 µg/week and RBV at 800 mg/day. Nineteen started treatment and 14 were available for an assessment at 24 weeks after the end of therapy. The SVR for this group was high at 71% given few dropouts and exclusions. In addition to the high SVR, the authors reported that no patients required dose adjustments due to adverse events.

A cost-benefit analysis for treatment of chronic HCV in co-infected patients examined the relative benefit of treatment with PEG-IFN alone, or with RBV versus treatment with unmodified interferon (Kuehne et al., 2002). The quality-of-life benefit was estimated using aversion of progression to cirrhosis with the decrement being the associated side effects of drug treatment. This was applied to a hypothetical cohort of 1 million HIV-positive adult patients with a mean CD4 cell count greater than 350 and uncompensated liver disease. Treatment with either interferon product benefited patients, with an increase in Quality Adjusted Life Years (QALY) ranging between 6.2 and 13.9 months for any genotype. For all genotypes, the use of unmodified interferon plus RBV in patients with moderate liver disease came at a cost benefit of \$50,000 per QALY. Patients infected with HCV genotype 1 and treated with PEG-IFN plus RBV have better clinical outcomes and subsequently an additional 1.6 quality-adjusted life months at a cost of \$40,000 per QALY. For HCV non-genotype 1, where clinical outcomes are similar between pegylated and unmodified interferon products at a much higher drug cost for the pegylated product, there is a benefit of only three additional weeks at an inequitably high cost, \$105,300 per QALY. The authors identified that further cost benefits could be realized if it is ever definitively demonstrated that treatment of HCV in HIV co-infected patients results in improved tolerance of antiretroviral medications.

Guidelines now favor the use of PEG-IFN-alpha-2a plus RBV over regimens with unmodified interferon-alpha-2a or regimens without RBV in the management of HIV/HCV co-infected patients. The time to start therapy remains controversial. Lee and Dieterich (2004) recommend initiation of HCV therapy for patients with higher CD4+ cell count (>350 cells/mL), with evidence of HCV-related liver disease (fibrosis) or when patients cannot maintain antiretroviral therapy due to recurrent drug-induced hepatotoxicity. Others suggest starting therapy in patients with higher CD4 cell counts, before the initiation of HAART to avoid drug interactions and additive toxicities. The HIV-HCV International Panel recommends treatment for any HIV co-infected patient with a CD4+ cell count >350 or with a CD4+ cell count between 200 and 350 with consideration of response based on HCV genotype and viral load. Deferral of therapy is recommended in those with a CD4+ cell count <200 (Soriano et al., 2004b). In patients already receiving HAART, those regimens that include didanosine (ddI) should be substituted with another drug given the increased risk of mitochondrial toxicities, particularly when used in combination with RBV (Mauss et al., 2004). As discussed, there are benefits to longer treatment durations unique to this co-infected group. Treatment beyond 24 weeks in patients without a 12-week response (EVR) is generally not beneficial (Strader et al., 2004; Alberti et al., 2005; Sulkowski, 2006). However, unlike the mono-infected subject, for patients with a 12-week response, a 48-week treatment should be considered, regardless of the genotype, including genotypes 2 and 3. No conclusion can be made regarding the choice of pegylated product as no randomized trial has been performed to compare PEG-IFN-alpha-2a with PEG-IFN-alpha-2b in the HCV/HIV co-infected population. More frequent and more diligent monitoring of these patients is in order, with careful consideration of the implications of the individual antiretroviral combination and use of adjuvant drugs to support cell lines.

Adverse Event Profile

Second only to nonresponse to therapy, drug-related adverse events are often the primary reason for discontinuation of PEG-IFN therapies. While the incidence of some adverse events, such as myalgias, fever, and general malaise, may be less than with unmodified interferon, the pegylation of IFN does not protect patients from other adverse events. These include the more debilitating neuropsychiatric and hematologic adverse events (Fried et al., 2002). A black box warning regarding such reactions is described in each of the manufacturer's product package inserts. Careful screening of patients before initiating therapy with frequent followup of core laboratory findings may decrease the need to alter or discontinue therapy due to adverse events. Some adverse events may be managed with dose reductions and/or supportive treatments. A summary of common types of drug-related adverse events appears in Table 5.

In controlled trials of PEG-IFN versus unmodified interferon preparations (Zeuzem et al., 2000; Heathcote et al., 2000), protocol-defined dose reductions were required in up to 32% of PEG-IFN-alpha-2a treated patients, compared with

Table 5 Common and Clinically Significant Side Effects of Pegylated Interferon Therapies [(pegylated IFN alpha-2a- Pegasys™) (pegylated IFN alpha-2b-Peg Intron™)]

Appearance-Related/Skin	Hematologic Effects
Alopecia	Neutropenia (both lymphocytic and neutrophilic)
Eczema	Anemia (more pronounced with co-treatment with ribavirin)
Pruritis	Thrombocytopenia
Rash	
Dry skin	
Cardiovascular	Neurologic/Behavioral
Angina	Aggression
Cardiomyopathy	Anxiety
Hypertension	Bipolar symptoms
Myocardial Infarction	Depression
	Dizziness
	Headache
	Hearing loss
	Impaired concentration
	Mania
	Neurocognitive impairments
	Suicidal ideation
	Vision changes
Endocrine	
Diabetes	
Hypo/hyperthyroidism	
Gastrointestinal	
Colitis	
Decreased appetite	
Diarrhea	
Hepatic decompensation	
Asterixis	
Elevated liver transaminases (ALT/AST)	
Elevated bilirubin	
Decreased albumin	
Decreased total protein	
Encephalopathy	
Increased prothrombin time	
Increased INR	
Nausea	
Upper abdominal pain	
Vomiting	
General	
Influenza-like symptoms	
Cough	
Fatigue	
Fever	
Myalgia	
Rigors	
Pneumonitis	

up to 27% of those treated with unmodified interferon. The primary concern about dose reduction is that while it may allay adverse events, it can also allow for incomplete suppression or eradication of the virus, as described by Fried (2000). The length of therapy also plays a role in the frequency and severity of adverse events. Drug discontinuation secondary to adverse drug events was recorded at higher rates in patients treated for 48 weeks (15%) versus those treated for 24 weeks

Table 6 Treatment Discontinuation of Standard IFN Versus PEG-IFN Due to Clinical Adverse Events or Lab Abnormalities^a

Trials and Comparative Arms	Standard IFN Group	PEG-IFN Group
Mono-Infection Trials		
Discontinuation Rates (%)		
Zeuzem et al. (2000)(PEG-IFN alpha-2a vs. unmodified IFN alpha-2a)	7	10
Heathcote et al. (2000)(PEG-IFN alpha-2a 90 mcg/wk vs. 180 mcg/wk vs. unmodified IFN alpha-2a)	10	90 mcg wk 11180 mcg wk 14
Fried et al. (2002)(PEG-IFN alpha-2a vs. unmodified IFN alpha-2a)	10	10
Pockros et al. (2004)(PEG-IFN alpha-2a 135 mcg/wk vs. 180 mcg/wk vs. unmodified IFN alpha-2a)	11	135 mcg/wk 9180 mcg/wk 10
Hadziyannis et al. (2004)(PEG-IFN alpha-2a + ribavirin 800 mg/day vs. PEG-IFN alpha-2a + ribavirin 1000 mg/day)	NA	Ribavirin 800 mg/d16 Ribavirin 1000 mg/d15
Manns et al. (2001)(PEG-IFN alpha-2b vs. unmodified IFN alpha-2b)	13	1.5 mcg/kg wk 140.5 mcg/kg wk 13
HIV/HCV Co-infection Trials		
ACTG 5071, Chung et al. (2004)(PEG-IFN alpha-2a vs. unmodified IFN alpha-2a)	12	12
RIBAVIC, Carrat et al. (2004)(PEG-IFN alpha-2b vs. unmodified IFN alpha-2b)	17	16
APRICOT, Torriani et al. (2004)(PEG-IFN alpha-2a vs. unmodified IFN alpha-2a)	14	12

^a Discontinuation rates were similar between PEG-IFN and standard interferon. Higher doses of ribavirin were associated with slightly higher rates of discontinuation. Additionally, the discontinuation rate was slightly higher among patients co-infected with HIV.

(5%). Drug discontinuation related to adverse drug events overall are compared in Table 6 for unmodified interferon versus PEG-IFN-based therapies from the larger randomized trials. The primary reasons for drug discontinuation were hematologic abnormalities and neurocognitive disorders. A higher rate of discontinuation is noted in the patients with HIV co-infection. Dose reductions are only slightly higher with longer treatment courses, 30% versus 33% as noted in the Food and Drug Administration briefing document (2002).

Constitutional symptoms resembling influenza-like illness have been noted in up to 51% of patients treated with PEG-IFNs (Zeuzem et al., 2000; Heathcote et al., 2000). Symptoms are often transient, and patients tend to develop tolerance over time. In the larger comparative trials, influenza-like symptoms occurred more frequently in patients treated with unmodified interferon plus RBV than with PEG-IFN plus RBV; 50% compared with 42% (*P* = 0.02) (Fried et al., 2002; Zeuzem et al., 2000).

Neuropsychiatric disorders, such as anxiety and depression, affect up to 26% of patients during treatment with PEG-IFN products. A warning exists for all interferon products regarding the potential new onset or exacerbation of neuropsychiatric disorders, including depression, suicidal ideation, increased addictive behaviors,

bipolar symptoms, mania, and aggressive behaviors. This warning is especially emphasized in patients with underlying neuropsychiatric disorders, particularly if they are not being treated or monitored for these conditions. A hypothesis for this adverse event was studied by Schwaiger (2003), wherein serotonergic activity in patients treated with PEG-IFN was measured and greatly reduced in those treated with the drug. Byrnes (2005) reported on a pre and post-evaluation of 10 patients treated with PEG-IFN to evaluate the potential confounding effect of HCV on neuronal function. They performed baseline brain MRI and 1H-MRS (spectroscopy), measurements of neurotransmitters, in addition to neuropsychological evaluation (neuropsychometric tests, Beck's depression inventory, and quality-of-life and self-reported cognitive dysfunction questionnaires) prior to, and 12 weeks following, initiation of PEG-IFN. The study demonstrated that as HCV viral load was reduced, there was a reduction in inflammatory markers, but depression scores increased and cognitive function declined. A history of depression is directly correlated with a higher incidence of drug-related psychiatric events during PEG-IFN therapy (Castera et al., 2004). However, there are some differences relative to unmodified interferon products. In the trial by Fried et al. (2002), depression was observed less frequently in the PEG-IFN-treated group compared with those treated with unmodified IFN-alpha-2b (22% vs. 30%, $P = 0.01$). Other trials confirmed this pattern (Zeuzem et al., 2000; Heathcote et al., 2000), although significantly morbid depression has been described in patients receiving either product. In parallel, the dose finding trial by Pockros et al. (2004) demonstrated a similar rate of depression for patients treated with PEG-IFN product versus unmodified interferon. Neurocognitive decline, such as decreased alertness, attention deficits, decreased vigilance, and impaired short-term memory, was demonstrated in a cohort of 70 patients treated with PEG-IFNs by Krauss (2005). Overall, neuropsychiatric disorders, including depression, mark the highest-ranking reason for drug withdrawal, particularly in those patients treated for 48 weeks versus 24 weeks (FDA brief, 2002).

Bone marrow suppression, resulting in low cell counts, such as anemia and neutropenia, is another common treatment-limiting adverse event of PEG-IFN therapies. This results from direct inhibition of progenitor cell proliferation in the bone marrow by interferon (Ganser et al., 1987). Initial laboratory data should be recorded as a baseline for the absolute neutrophil count, hemoglobin, and platelets. Patients with low counts at baseline (a neutrophil count $<1,500$ cells/mm³ or a baseline hemoglobin <10 g/dL or a baseline platelet count $<90,000$ cells/mm³) should be treated cautiously with lower starting doses of PEG-IFN and careful monitoring of cell lines during therapy. Severe, persistently low counts may result in infectious complications including opportunistic infections. Therapy with PEG-IFN should be interrupted or discontinued if counts do not respond to dose modifications.

Hematologic abnormalities are the most common reason for dose modifications in many of the trials (Fried et al., 2002; Chung et al., 2004; Torriani et al., 2004; Pockros et al., 2004; Carrat et al., 2004). Drug-related neutropenia can begin early, with a nadir in the first four weeks of therapy. Rates of neutropenia have been reported to be higher in patients treated with PEG-IFN products than with unmodified interferon in randomized trials (Fried et al., 2002; Chung et al., 2004; Torriani et al., 2004; Carrat et al., 2004; Heathcote et al., 2000). Neutropenia defined as

grade 4 (ANC < 500/mL) has been documented in multiple trials. Dose reductions are employed in up to 11% of the patients treated with the PEG-IFN versus 7% of patients receiving unmodified interferon. In an analysis of the effects on hematologic cell lines, Schmid (2005) analyzed 133 patients undergoing treatment with unmodified interferon, unmodified interferon plus RBV, PEG-IFN-alpha-2a plus RBV, or PEG-IFN-alpha-2b plus RBV. Leukopenia was common to all arms. The maximum decrease in neutrophils and lymphocytes occurred in patients treated with PEG-IFN products, 55% for PEG-IFN-alpha-2a and 52% for PEG-IFN-alpha-2b versus 37% for unmodified IFN ($P < 0.05$). As an exception, the trial by Heathcote (2000) demonstrated similar rates of grade 4 neutropenia among groups (3% with unmodified interferon, 3% and 1% with the PEG-IFN-alpha-2a at 90 and 180 $\mu\text{g}/\text{wk}$). Dose reductions for PEG-IFN-alpha-2a to 135 $\mu\text{g}/\text{week}$ from 180 $\mu\text{g}/\text{week}$ and to 0.75 $\mu\text{g}/\text{kg}/\text{week}$ from 1.5 $\mu\text{g}/\text{kg}/\text{week}$ for PEG-IFN-alpha-2b are recommended when the ANC falls below 750. Treatment discontinuation is recommended if the ANC falls below 500.

Thrombocytopenia has been observed, particularly early in treatment (within 2 weeks). Similar comparative rates of thrombocytopenia in the trial by Fried (2002) were observed between patients receiving PEG-IFN-alpha-2a plus RBV, or PEG-IFN-alpha-2a plus placebo as compared to unmodified interferon plus RBV at 4% versus 6% versus <1%, respectively. Severe thrombocytopenia, classified as grade 3, or a platelet count between 20,000 and 50,000/mL, occurred equally between unmodified and PEG-IFN products in the study by Zeuzem (2000). One HIV/HCV co-infection study (Chung et al., 2004) described two patients with grade 4 thrombocytopenia (<20,000/mL), one in the unmodified and one in the PEG-IFN-treated groups. However, the study by Heathcote et al. (2000) demonstrated a higher incidence of thrombocytopenia in patients receiving PEG-IFN-alpha-2a, 26% versus 7% of all patients treated with unmodified interferon ($P < 0.001$, $P = 0.04$, respectively). In an observational crossover study, Homincik (2003) examined the effects of one dose of unmodified interferon-alpha-2a followed by weekly PEG-IFN-alpha-2a for 36 weeks on both platelet count as well as platelet activity. Decreases in platelet count were noted uniformly, but platelet activity was relatively unchanged. In the analysis of drug-related hematologic effects of six prospective trials by Schmid (2005), median decreases in platelet counts were similar in the patients treated with unmodified interferon alone (25%) versus those treated with PEG-IFN products plus RBV, 21% for PEG-IFN-alpha-2a and 23% for PEG-IFN-alpha-2b. An unusual case of late-onset (six months after drug discontinuation) drug-related autoimmune thrombocytopenia (PEG-IFN-alpha-2b plus RBV) was reported by Elefsiniotis (2006). Drug-related thrombocytopenia was not associated with increased bleeding episodes in any of the major trials, but when thrombocytopenia is severe, the risk of bleeding rises proportionally. The presence of cirrhosis of the liver adds to this risk. Dose reductions for thrombocytopenia have been required in up to 21% of patients with cirrhosis versus 6% for the overall population in a monotherapy study group and 16% for cirrhotics versus 4% for the overall population in the combination study group (FDA Brief, 2002). Recovery of platelet counts occurs by four weeks after treatment is completed or discontinued. Dose reductions to 90 $\mu\text{g}/\text{week}$ from 180 $\mu\text{g}/\text{week}$ for PEG-IFN-alpha-2a are recommended if the platelet

count falls below 50,000. Therapy should be discontinued if the platelet count falls below 25,000.

Drug-related anemia has also been well documented, particularly in patients co-treated with RBV. Data relative to erythropoietin levels in treated patients indicate that patients cannot maintain erythropoietin levels adequate to offset treatment-related anemia (Balan et al., 2003). Hemoglobin values appear to decrease similarly when comparing PEG-IFN to unmodified interferon; in one study, they fell by a maximum of 3.7 g/dL for PEG-IFN-alpha-2a plus RBV, compared to 3.6 g/dL for unmodified interferon-alpha-2b plus RBV. However, when examining rates relative to the percent of patients whose hemoglobin falls below 10 g/dL, Schmid (2005) demonstrated higher rates among patients treated with PEG-IFN-alpha-2a with RBV (29%) versus 6% of patients treated with unmodified interferon-alpha-2b with RBV ($P < 0.05$). The common denominator remains the additive anemic effects mediated by ribavirin. The proposed mechanism is direct hemolysis by RBV as demonstrated by De Franceschi (2000). A handful of patients with HIV co-infection have had observed grade 4 anemia, Hgb less than 6.5 g/dL (Chung et al., 2004). All three hematologic abnormalities have been documented at higher rates in patients with a lower body mass index (BMI), perhaps reflecting the use of fixed doses of PEG-IFN-alpha-2a. High RBV blood levels and concomitant treatment with zidovudine have also been identified as predictors of treatment-related anemia (Rendon et al., 2005). Treatment should be discontinued if the Hgb falls below 8.5 g/dL.

New onset cardiovascular dysfunction has been documented rarely (21 total reported cases) in patients treated with unmodified interferon (Kuwata et al., 2002; Cohen et al., 1990; Sonnenblick et al., 1990). These conditions include cardiomyopathy, myocardial infarction, angina, and hypertension. A baseline EKG and serial monitoring in patients with pre-existing cardiovascular disease are recommended. Risk reduction measures should also be considered in patients at a high risk for cardiovascular complications. A recent case report by Condat (2006) details a case of fatal cardiomyopathy in a patient receiving PEG-IFN/RBV therapy.

Ocular changes have been described with unmodified interferon treatment of hepatitis C and newly with PEG-IFN-alpha-2b (Farel et al., 2004; Ahmed et al., 2003; Schulman et al., 2003). In the case series review by Farel (2004), patients co-infected with HIV and HCV who were treated with PEG-IFN-alpha-2b plus RBV underwent serial ophthalmologic exams every three months, revealing pathology in 35% of the patients. These included cotton wool spots, cataracts, and decreased red-green color vision. The color vision changes were reversed in one patient 10 weeks after discontinuation of combination therapy. The other patient had sustained visual changes from weeks 10 through 23 of therapy. Visual changes spontaneously resolved. None of the patients had diabetes or hypertension. Speculation of the underlying mechanism for this side effect lies in an observational study by Sugano (1998) wherein the authors measured plasma levels of complement 5a that revealed a drug-induced increase in plasma levels of complement 5a. Complement 5a is purported to deposit in the retinal vasculature, leading to local capillary rupture. Baseline and a followup ophthalmologic exam are recommended based on these data.

Interferon treatment for chronic HCV infection may exacerbate or result in hepatic decompensation, particularly in patients co-infected with HIV and receiving highly active antiretroviral therapy (HAART). A baseline liver biopsy and serial laboratory panels for liver injury (serum AST/ALT, total bilirubin) and synthetic function (albumin, PT, INR, total protein) are recommended. An analysis of risk factors for development of hepatic decompensation was performed for the APRI-COT trial by Torriani (2004). All patients had advanced cirrhosis as a predisposing factor. Additional risk factors were co-treatment with didanosine and evidence of cholestasis at baseline. Adverse events include potentially acute liver transaminase flares, elevations in bilirubin, and evidence of decompensation (e.g., encephalopathy, elevated bleeding times, asterixis).

Thyroid disorders have been linked to unmodified interferon and PEG-IFN therapy (Imigawa et al., 1995; Fonseca et al., 1991; Preziati et al., 1995; Lisker-Melman et al., 1992). Induction of anti-thyroid antibodies and autoimmune thyroiditis is the primary mechanism by which hypothyroidism is induced by interferon products. A baseline TSH and a followup TSH are recommended in the Veteran's Health Administration guidelines (2005). Some patients require supplementation with levothyroxine.

Allergy or drug hypersensitivity is a rare event linked to PEG-IFN use. Like other drugs, the reaction is not predictable and may manifest itself as an acute IgE-mediated event, with urticaria, hypotension, and anaphylaxis. Anti-IFN antibodies have been positive in a handful (4.8%) of patients in the larger trials (Fried et al., 2002), but no notable sequelae were observed as a result. Skin rashes have been documented in multiple trials. A severe skin rash was described in a case series by Jessner (2002) wherein three patients using PEG-IFN developed a delayed rash requiring drug discontinuation. Two of the three patients were switched to unmodified interferon therapy with resolution and without recurrence of the rash. The third patient was not rechallenged.

Other notable case reports include a documented interstitial pneumonitis with adult respiratory distress syndrome (Abi-Nassif et al., 2003). The patient described had no previous history of pulmonary disease but, upon presentation, required admission to the intensive care unit. The patient died 26 days after admission, of bacteremia and fungemia. The mechanism of this potentially related AE is unknown but may be secondary to a localized autoimmune response to the medication.

Appearance-related side effects include alopecia, dry skin, and injection site reactions. Decreased appetite leading to weight loss and anorexia are also reported. Drug-induced eczema and other skin disorders secondary to interferon therapies have been well documented (Moore et al., 2004; Shen et al., 2005; Dalekos et al., 1998; Dereure et al., 2002). Hyperpigmentation has been described of the tongue and skin, particularly in dark-skinned non-Caucasian patients (Gurguta et al., 2005). Other notable dermatological diseases noted with interferon therapy include cutaneous sarcoidosis and psoriasis, as described and reviewed recently by Hurst and Mauro (2005) and Ketikoglou (2005), respectively.

Adverse events attributed to PEG-IFNs can be difficult to manage, requiring dose adjustments and potentially drug discontinuation. A summary of discontinuation rates in some of the major trials, including the HIV co-infection trials,

appears in Table 6. Discontinuation rates were notably higher in the co-infection trials due to a higher frequency of drug-related adverse events. The addition of preemptive agents or drugs to treat or palliate adverse drug effects while continuing PEG-IFN is an option. These include granulocyte cell-stimulating factor or granulocyte-macrophage colony-stimulating factor for neutropenia (Lebray et al., 2005), oprelvekin (NEUMEGA[®]) for thrombocytopenia, erythropoietin for anemia (Afdhal et al., 2004; Sulkowski et al., 2005; Shiffman et al., 2005), and selective serotonin reuptake inhibitors (Krauss et al., 2002) for depression.

Teratogenicity

Peginterferons are classified as pregnancy category C when used without RBV. The addition of RBV increases the severity of this classification to category X (PEGASYS[®] and PEG-INTRON[®] package inserts). Little to no collaborative data are available on the safety of PEG-IFNs in humans or animals during pregnancy. In Rhesus monkeys, unmodified interferon administered at 20 to 500 times the human weekly dose was associated with no teratogenic events. No information is currently available on the distribution of PEG-IFNs into breast milk, and as such, there are no published data on the safety of the drug in the breastfed child.

Conclusion

The pegylation of the interferon molecule represents a significant breakthrough in the management of chronic HCV infection when compared with unmodified interferon. The therapeutic effect is especially obvious when the pegylated interferons are combined with RBV. In addition, pegylation of interferon allows for less frequent administration, which may improve adherence to therapy. Despite extensive research, efforts to improve the SVR rate for subjects infected with genotypes 1 and 4 above the current 40–50% and 61–69% levels remains elusive. The likelihood of attaining an SVR in subjects infected with HCV genotype 2 or 3 with combination therapy with PEG-IFN/RBV regimens is excellent. However, new data indicate that response to therapy of genotype 3 may be less than that of genotype 2. More research is under way to address the issue of difficult-to-treat patients including subjects who do not respond to treatment or relapse after an end-of-treatment response. Other difficult-to-treat patients include African Americans as well as subjects undergoing liver transplantation. New guidelines to manage HCV co-infection in patients with HIV disease have been developed. Improved attention to adverse events has allowed patients to continue therapy and complete more of therapy, thus improving the chance of achieving an SVR. The combination of PEG-IFN products with new agents that attack hepatitis C in a variety of different sites appear promising, and we await the completion of phase III studies.

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