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Pharmacokinetics and Pharmacodynamics of Peginterferon and Ribavirin: Implications for Clinical Efficacy in Treatment of Chronic Hepatitis C

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Pharmacokinetics; pharmacodynamics; peginterferon alfa-2a; peginterferon alfa-2b; ribavirin and chronic hepatitis C

Introduction

More than 3.2 million people in the United States and greater than 200 million people worldwide are chronically infected with hepatitis C virus and are at risk for the development of cirrhosis, decompensated liver disease and hepatocellular carcinoma.¹ Therapy of chronic hepatitis C infection has improved from 10% to 20% with regimens using standard interferon alfa monotherapy^{2–4} to 54% to 56%, with regimens that use peginterferon in combination with ribavirin.^{5–7} Thus, the current standard of treatment for chronic hepatitis C is the combination of a peginterferon with ribavirin administered for a duration of 24 or 48 weeks depending on the infecting hepatitis C genotype.⁸ Two pegylated interferons are approved for the treatment of chronic hepatitis C, peginterferon alfa-2a and peginterferon alfa-2b. These compounds differ in their size and the type of pegylation resulting in different pharmacokinetics and pharmacodynamics for each compound. This chapter will focus on how the different properties of these compounds impact on their *in-vivo* performance and clinical efficacy.

Formulation of Peginterferon alfa-2a and Peginterferon alfa-2b

Pegylation is a process whereby polyethylene glycol (PEG) polymer chains are covalently attached to another molecule, normally a drug or therapeutic protein. In general, pegylation results in improved pharmacokinetic and pharmacodynamic properties, increased drug stability, increased overall circulation life-span and changes to tissue distribution pattern and elimination pathways.⁹ The molecular weight, configuration, (linear or branched) and means of attachment of the PEG moiety are the primary contributors to the physicochemical properties of the PEG-peptide conjugate. Attachment of PEG at multiple sites can lead to steric interference between the compound and its receptor, which may reduce the biological

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activity of the conjugate.⁹ Pegylated interferon alfa-2a consists of a branched, 40-kD PEG moiety covalently attached to an interferon alfa-2a molecule.¹⁰ Pegylated interferon alfa-2b consists of a 12 kD linear PEG molecule covalently attached to interferon alfa-2b.¹¹ There are several advantages of a branched PEG formulation over a linear PEG one. For two PEG molecules of the same molecular mass, a branched PEG acts as if it were much larger than a corresponding linear PEG. Branched-chained PEG conjugates also have greater thermal and pH stability, are more resistant to proteolytic degradation and less antigenic because of shielding of the attached polypeptide from the immune system.⁹ Key differences in the formulation of peginterferon alfa-2a and alfa-2b are summarized in Table 1.

Pharmacokinetics of Peginterferon

The difference in pegylation between the two peginterferons has a significant impact on their pharmacokinetic properties. Peginterferon alfa-2b has a relatively rapid absorption with a half-life of 4.6 hours and a volume of distribution of 0.99L/Kg, which are not significantly different from that of standard interferon alfa-2b, 2.3 hours and ~1.4L/Kg respectively.¹¹ Maximum serum concentrations are achieved between 15 and 44 hours post-dosing and are sustained for 48 to 72 hours, with a peak to trough ratio of >10 after multiple doses.¹¹ However, mean apparent clearance for pegylated interferon- α 2b (22 mL/h/kg) is approximately one tenth that of nonpegylated interferon- α 2b (231 mL/h/kg).¹¹ Thus, the observed increase in clinical efficacy of peginterferon alfa-2b is principally the result of reduced renal clearance, rather than of effects on pegylation on rate of absorption or distribution.

Peginterferon alfa-2a is absorbed more slowly than peginterferon alfa-2b and has a restricted volume of distribution (confined largely to the vasculature and liver). A single dose of 180 μ g in healthy volunteers produced a mean maximum serum concentration of 14.2 μ g/L, which was reached in a mean time of 78 hours.¹² After multiple doses of peginterferon alfa-2a (180 μ g q weekly) in patients with chronic hepatitis C, the mean maximum serum concentration was 25.6 μ g/L and this was achieved in a mean time of 45 hours.¹² Peginterferon alfa-2a has a lower peak to trough ratio (1.5 to 2) compared to peginterferon alfa-2b, indicating that there is less fluctuation in the serum concentration of the drug during the one week dosing interval. Peginterferon alfa-2a is cleared by both the kidney and liver. Because of its relatively large size, peginterferon alfa 2a has more than a 100-fold reduction in renal clearance compared to interferon alfa-2a. The pharmacokinetics of the drug is unaffected by renal failure, so no dose modifications are necessary in the setting of renal impairment as compared to peginterferon alfa-2b.¹³

Head-to-head comparison of the two peginterferons indicated that peginterferon alfa-2b has a shorter half-life in serum compared to peginterferon alfa-2a. A significant proportion of patients receiving peginterferon alfa-2b have levels of drug below the limits of detection by the end of day 7.^{14, 15} Low serum concentrations towards the end of the dosing schedule may be associated with viral rebound. These observations suggest that a shorter dosing interval may be necessary for peginterferon alfa-2b. Indeed, one study has reported improved viral kinetics with a twice weekly regimen but SVR rates were not reported and a formal study has not been conducted.¹⁶

Pharmacokinetics of Ribavirin

Bioavailability of ribavirin was assessed in six healthy volunteers using an intravenous formulation containing 150 mg of intravenous ¹³C3-ribavirin followed 1 h later by a 400-mg oral dose of ribavirin. The mean maximum concentrations of drug in plasma for intravenous and oral ribavirin were 4,187 and 638 ng/ml, respectively.¹⁷ The mean bioavailability was 51.8% $\pm$ 21.8%, and the mean γ -phase half-life was 37.0 $\pm$ 14.2 h. The mean renal clearance,

metabolic clearance, and volume of distribution of the central compartment were 6.94 liters/h, 18.1 liters/h, and 17.8 liters, respectively.¹⁷ There does not appear to be any evidence that peginterferons alter the pharmacokinetics of ribavirin.¹⁸ Following administration of ribavirin doses of 600, 800, 1000 to 1,200 mg daily in combination with peginterferon alfa-2b, mean peak plasma ribavirin concentrations at week 1 were 741 ng/mL, 799 ng/mL and 1101 ng/mL, respectively. Mean time to mean peak plasma levels occurred between 1 and 2 hours after dosing. Mean peak plasma ribavirin concentrations at week 4 were 1770 ng/mL, 2297 ng/mL and 2750 ng/mL for patients treated with 600, 800, 1000 to 1,200 mg of ribavirin daily in combination with peginterferon alfa-2b, respectively, ribavirin are achieved by most patients by 4 weeks.¹⁸

Pharmacodynamics of Peginterferon

Interferon has both direct and indirect antiviral actions against the hepatitis C virus. It is not exactly certain how interferon alfa eradicates hepatitis C virus infection. Interferon mediates its antiviral effect by inducing interferon-stimulated genes (ISGs) which encode for a number of effector proteins with antiviral effects such as protein kinase (PKR), 2', 5' oligoadenylate synthetase, adenosine deaminase (ADAR) and protein GTPase MX leading to inhibition of mRNA translation, RNA degradation and editing and production of nitric oxide.^{19, 20} Interferon alfa may also act indirectly via upregulation of MHC Class I genes on antigen presenting cells promoting cytotoxic T cell clearance of virally infected cells.²⁰

Peginterferon alfa-2b can be considered a pro-drug of interferon alfa-2b. The urethane bond linking the 12 kDa PEG chain to interferon in peginterferon alfa-2b is unstable and susceptible to hydrolysis such that following injection, native interferon alfa-2b is released and circulates in the body. In contrast, the amide bond linking the PEG chain to interferon alfa-2a is not subject to hydrolysis. Overall, the *in-vitro* antiviral activity of peginterferon alfa-2a is approximately 7% of interferon alfa-2a¹⁰ whereas antiviral activity of peginterferon alfa-2b is approximately 28% of interferon alfa-2b.²¹ This may be in part due to reduced affinity of peginterferon alfa-2a for its receptor *in vitro* because of the more stable covalent linkage of the PEG moiety.

Biological activity of interferon alfa may be estimated by measuring levels of ISGs or known endogenous proteins induced by interferon such as 2'5' oligoadenylate synthetase (2'5' OAS), neopterin and β_2 -microglobulin. Serum levels of 2'5' OAS were shown to increase rapidly following single doses of standard interferon alfa-2a and peginterferon alfa-2a and to peak 24 or 48 hours after administration.²² 2'5' OAS levels declined rapidly in recipients of standard interferon alfa-2a but remained near peak levels for 1 week in recipients of pegylated interferon alfa-2a.²² Similarly, administration of peginterferon alfa-2b was associated with dose-related increases in serum neopterin levels and non-dose related increases in serum 2'5' OAS levels in patients with chronic hepatitis C.¹¹

Pharmacodynamic studies comparing the two peginterferon preparations have yielded conflicting results. In one small study, 22 patients were randomized to receive either peginterferon alfa-2a 180 μ g weekly or peginterferon alfa-2b 1.0 μ g weekly.²³ The enzymatic activity of 2'5' OAS, neopterin and β_2 -microglobulin were measured over a 7 day period. 2'5' OAS activity, serum neopterin and beta(2)-microglobulin concentrations did not differ significantly between the two patient groups at any time point, nor was there a significant correlation between the serum area under the concentration-time curve of either peginterferon and the area under the concentration-time curve for 2',5'-oligoadenylate synthetase, neopterin and beta(2)-microglobulin.²³ In contrast, in another study, thirty-six patients were randomized to peginterferon alfa-2b (1.5 lg/kg/week) or peginterferon alfa-2a (180 lg/week) for 4 weeks, then in combination with ribavirin (13 mg/kg/day) for a further 4

weeks.²⁴ The pharmacokinetic profile of both peginterferons, mRNA expression of a selected group of ISG transcripts, and serum hepatitis C virus RNA levels were assessed. Patients receiving peginterferon alfa-2b had significantly greater up-regulation of interferon-alfa response genes compared with those receiving peginterferon alfa-2a. Correspondingly, patients treated with peginterferon alfa-2b also had a significantly greater log10 maximum and log10 time-weighted average decrease in serum hepatitis C virus RNA levels. Differences in measures of interferon's effectiveness, enzymatic assays compared to mRNA levels and differences in study design may account for the differences in results. Pharmacodynamics of peginterferon alfa-2a does not appear to be affected by race.²⁵

Safety of Peginterferons

Interferon alfa-2a or 2b is associated with a range of side effects. The early side effects include influenza like symptoms (fever, chills, myalgia, fatigue and arthralgia) dermatological (rash) and bone marrow suppression (neutropenia, anemia and thrombocytopenia). The later complications include neuro-psychiatric, cardiovascular, autoimmune and infectious side effects. Peginterferons have similar side effect profiles as standard interferons. Several head-to-head studies have demonstrated similar safety and tolerability profiles between the two peginterferons.²⁶⁻²⁸ One of the larger trials, The Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study, reported discontinuation rates of peginterferon alfa-2a and 2b for adverse events of 13% and 12.7%, respectively.²⁶ Rates of grade 2 (hemoglobin <10 g/dL) and grade 3 (hemoglobin <8.5 g/dL) anemia were similar between peginterferon alfa-2a and 2b, 29.6% versus 30.7% and 3.8% versus 2.5%, respectively.²⁶ Mild (<750/mm³) and moderate (<500/mm³) neutropenia was significantly different between the two preparations, 27% versus 22.2% and 5.9% versus 2.8%, in the Ideal study²⁶ but not in two randomized, Italian studies.^{27, 28} Although in the later studies, patients receiving peginterferon alfa-2a were more likely to require dose reduction for neutropenia. A recent meta-analysis of adverse events leading to treatment discontinuation in 11 head-to-head trials comparing peginterferon alfa-2a and peginterferon alfa-2b revealed no significant differences between the two peginterferons.²⁹

Clinical Efficacy of Combination Peginterferon and Ribavirin: Week 4 and 12 Viral kinetics

Measurement of the rate of clearance of virus from serum during therapy is a strong predictor of treatment response.³⁰ Patients who achieve a rapid virological response (RVR), defined as an undetectable test for HCV RNA by treatment week 4 have a high likelihood of obtaining a sustained virological response (SVR), >80%. In contrast, the absence of an early virological response (EVR), defined as ≥ 2 log reduction in HCV RNA from baseline or testing HCV RNA negative by treatment week 12, is the best predictor of a lack of SVR.⁸ Thus, comparing week 4 and 12 viral kinetics provides a means of comparing the clinical efficacy of the two peginterferon preparations. RVR rates appear to be similar between the two peginterferon preparations.^{27, 28, 31} In one study, rates of RVR were reported as 29% for patients treated with peginterferon alfa-2b and 24% for those treated with peginterferon alfa-2a.³¹ In the IDEAL study (see below) RVR rates did not differ between the standard dose peginterferon alfa-2b and peginterferon alfa-2a arms 12.2% versus 12.1%, respectively. In contrast, EVR rates appear to be significantly higher with peginterferon alfa-2a. In the IDEAL trial, EVR rates were 45% in the peginterferon alfa2a arm and 39.9% in the peginterferon alfa-2b arm.²⁶ In another trial of 320 consecutive, treatment-naïve, subjects with chronic hepatitis C randomly assigned to once weekly peginterferon alfa-2a (180 µg, group A) or peginterferon alfa-2b (1.5 µg/kg, group B) plus ribavirin 1000 mg/day (body weight <75 kg) or 1200 mg/day (body weight >75 kg) for 48 weeks (genotype 1 or 4) or 24

weeks (genotype 2 or 3) reported significantly higher EVR and complete EVR rates in HCV genotype 1 patients treated with peginterferon alfa 2a compared to peginterferon alfa-2b.²⁸ Thus, the emerging data suggests that the branched peginterferon formulation appears to be associated with better viral clearance by week 12.

SVR

The IDEAL study was designed to compare standard-dose and low-dose regimens of peginterferon alfa-2b, plus ribavirin, after it was observed that both dose levels yielded similar rates of sustained virologic response in the absence of ribavirin. A third treatment group, peginterferon alfa-2a plus ribavirin, was added to the study because it was the other approved regimen. Patients with HCV genotype 1 infection who had not previously been treated were randomly assigned to undergo 48 weeks of treatment with one of three regimens: peginterferon alfa-2b at a standard dose of 1.5 µg per kilogram of body weight per week or a low dose of 1.0 µg per kilogram per week, plus ribavirin at a dose of 800 to 1400 mg per day, or peginterferon alfa-2a at a dose of 180 µg per week plus ribavirin at a dose of 1000 to 1200 mg per day.²⁶ Among 3070 patients, rates of sustained virologic response were similar among the regimens: 39.8% with standard-dose peginterferon alfa-2b, 38.0% with low-dose peginterferon alfa-2b, and 40.9% with peginterferon alfa-2a ($P = 0.20$ for standard-dose vs. low-dose peginterferon alfa-2b $P = 0.57$ for standard-dose peginterferon alfa-2b vs. peginterferon alfa-2a). The end of treatment response was significantly higher for peginterferon alfa-2a (64.4%) compared to standard dose peginterferon alfa-2b, 53.2%.²⁶ However, relapse rates were significantly higher among patients receiving peginterferon alfa-2a, 31.5% *versus* 23.5%. Different ribavirin dose and dose reduction schedules may have influenced relapse rates.

The results of the IDEAL study are quite convincing and are supported by several other studies. However, five recent studies including a meta-analysis suggested that peginterferon alfa-2a is associated with a significantly higher SVR rate compared to that of peginterferon alfa-2b plus ribavirin, Table 2.^{27–29, 32, 33} In one Italian study, 447 treatment-naïve patients with chronic hepatitis C were randomly assigned to receive either 1.5 mcg/Kg/week PegIFNalpha2b plus RBV 800–1200 mg/day or 180 mcg/week PegIFNalpha2a plus RBV 800–1200 mg/day for 24 or 48 weeks according to HCV genotype.²⁷ By intention to treat, the SVR rate was higher in patients assigned to peginterferon alfa-2a compared to peginterferon alfa-2b (66% vs 54%, respectively, $P = .02$). In another Italian study, 320 consecutive, treatment-naïve, patients with chronic hepatitis C were randomly assigned to once-weekly peginterferon alfa-2a 180 µg, or peginterferon alfa-2b 1.5 µg/kg plus weight-based ribavirin. The SVR rate was greater in the patients receiving peginterferon alfa-2a compared to peginterferon alfa-2b 68.8% vs 54.4%; $P = .008$). Subanalysis by genotype demonstrated that the higher SVR associated with peginterferon alfa-2a were observed across all genotypes,²⁸ but this was not confirmed in another study.²⁷ A third observational study evaluated the efficacy and tolerability of peginterferon alfa-2a compared with peginterferon alfa-2b plus weight-based ribavirin for the treatment of chronic hepatitis C in routine clinical practice, PRACTICE study, involving 23 German centers.³³ No difference in SVR rates were noted in the intent-to-treat cohort ($n=3414$) between peginterferon alfa-2a and peginterferon alfa-2b. 52.9% *versus* 50.5%, respectively. However, in a subanalysis of genotype 1-infected patients matched by baseline parameters and cumulative RBV dose, SVR rates were 49.6% and 43.7% for those receiving peginterferon alfa-2a and peginterferon alfa-2b, respectively ($P \leq 0.047$).³³ In addition, another retrospective, observational study of a large cohort ($n=9544$) of US veteran reported that treatment of genotype 1 patients with peginterferon alfa-2a was associated with an almost 50% higher likelihood of SVR than treatment with peginterferon alfa-2b. Finally, a recent meta-analysis of 12 randomized clinical trials ($n=5,008$ patients) that directly compared peginterferon

alpha-2a plus ribavirin to peginterferon alpha-2b plus ribavirin reported higher SVR rates with peginterferon alpha-2a compared to peginterferon alpha-2b, 47% *versus* 41%, respectively.²⁹ Peginterferon alpha-2a and peginterferon alpha-2b generally have similar clinical efficacy, however several recent trials suggests that peginterferon alpha-2a is associated with higher SVR than peginterferon alpha-2b. Further studies controlling for baseline features, using similar ribavirin dosing regimens will be needed to determine if there is indeed a difference in clinical efficacy.

In conclusion, the pharmacokinetics and pharmacodynamics of standard interferon alpha-2a and interferon alpha-2b are substantially altered by pegylation. The size, geometry and site of attachment of the PEG moiety impact the pharmacokinetics, pharmacodynamics as evidenced by the different absorption, volume of distribution and clearance of the linear 12 kDa peginterferon alpha-2b and the branched 40 kDa peginterferon alpha-2a. Despite these differences, the clinical efficacy, safety and tolerability of the two peginterferons appear to be quite similar. Although tantalizing evidence from recent studies suggest that peginterferon alpha-2 plus ribavirin may be associated with a small but significantly greater SVR rates compared to peginterferon alpha-2b. Carefully designed studies will be necessary to confirm whether a true difference exists between the two peginterferon preparations. This may be moot once the direct acting antiviral agents become available.

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Abbreviations

2' 5' OAS 2' 5' oligoadenylate synthetase

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Table 1

Comparison of the formulation of peginterferon alfa-2b and peginterferon alfa-2a

Characteristic	Pegintereron alfa-2b	Pegintereron alfa-2a
PEG Structure	Small, linear 12 kD mPEG	Two 20 kD mPEG chains, linked to form a large, branched 40 kD mPEG
PEG Conjugation	mPEG activated with succinimidyl carbonate (SC- PEG) resulting in potential reactions with several amino acids	mPEG activated with N- hydroxysuccinimide (PEG2-NHS) which attaches to lysine residues
Positional isomers	13	6
Protein bond	Major positional isomer (12 kDa PEG attached to HIS) has a hydrolytically unstable urethane (carbonyl) bond	Stable amide bond between mPEG and lysines on protein chain
Monopegylation	95%	95%
Stability	Stored as a powder; must be immediately reconstituted before injection	Stored as a solution, which is stable for at least 2 years

Table 2
Comparison of Clinical Efficacy of Peginterferon alfa-2a and Peginterferon alfa-2b for Patients with HCV Genotype 1

Author	Trial Design	Treatment Regimen	No.	ETR	SVR	RR
McHutchison et al 2009	RCT	PegIFN α-2a 180 µg	1035	64.4	40.9	31.5
		PegIFN α-2b 1.5 µg/kg	1019	53.2	39.8	23.5
Rumi et al 2010	RCT	PegIFN α-2a 180 µg	91	65	48	22
		PegIFN α-2b 1.5 µg/kg	87	44	32	26
Ascione et al 2010	RCT	PegIFN α-2a 180 µg	93*	75.3	54.8	20.4
		PegIFN α-2b 1.5 µg/kg	93	49.5	39.8	9.7
Mangia et al 2008	RCT	PegIFN α-2a 180 µg	334	61	49.1	19.6
		PegIFN α-2b 1.5 µg/kg	362	56.6	45.6	19.6
Backus et al 2007	Retro-spective	PegIFN α-2a 180 µg	2091		25 [#]	
		PegIFN α-2b 1.5 µg/kg	3853		18	
Withthoeft et al 2010	Retro-spective	PegIFN α-2a 180 µg	1784		49.6 [^]	
		PegIFN α-2b 1.5 µg/kg	1686		43.7	

Includes 4 and 1 patients with HCV genotype 4 randomized to peginterferon alfa-2a and 2b, respectively

[#] Overall SVR rates for all HCV genotypes were 31% and 25% for peginterferon alfa-2a and 2b, respectively

[^] Overall SVR rates for all HCV genotypes were 52.3% and 50.5% for peginterferon alfa-2a and 2b, respectively