

## Type of Pegylated Interferon Matters: Another Milestone in the Treatment of Hepatitis C Virus Infection

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Hepatitis C virus (HCV) infects 170 million people worldwide <sup>(1)</sup>. The infection becomes chronic in 85%–90% of cases with potential to cause cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC) <sup>(2)</sup>.

Treatment of HCV infection has evolved significantly over the last 20 years since the introduction of interferon- $\alpha$  in 1991. Initial studies using interferon were disappointing with response rates of less than 20%. Later, two important advances in the treatment of HCV infection, namely pegylation of interferon and introduction of ribavirin (RBV) in 2002, have revolutionized the treatment of HCV infection <sup>(3)</sup>. Pegylation is a process in which a polyethylene glycol (PEG) moiety is attached to the molecules used for the treatment <sup>(4)</sup>. This results in alteration of the pharmacokinetic, pharmacodynamic, and immunologic properties of

the drug which in turn results in longer duration of action of the pegylated molecule allowing for using lower doses of the drug and better efficacy. Two pegylated molecules of interferon are pegylated interferon (PEG-IFN)- $\alpha$ 2a (Pegasys) and - $\alpha$ 2b (PegIntron). Both these molecules differ in terms of their physical characteristics and pharmacological properties (Table 1) <sup>(5)</sup>. One of the major differences between these two molecules is that PEG-IFN- $\alpha$ 2b has a urethane bond which is unstable and is sensitive to hydrolysis. This results in release of interferon- $\alpha$ 2b (the main therapeutic molecule) after injection of PEG-IFN- $\alpha$ 2b. In contrast, PEG-IFN- $\alpha$ 2a with an amide bond is chemically stable and the entire intact molecule has therapeutic effects <sup>(5)</sup>. PEG-IFN- $\alpha$ 2a does not require any dose modification in the presence of renal insufficiency, in contrary to PEG-IFN- $\alpha$ 2b which requires dose

**Table 1.** Physical and pharmacological characteristics of the two studied pegylated interferons.

Characteristic	Peginterferon- $\alpha$ 2a	Peginterferon- $\alpha$ 2b
Structure	12 kDa molecule	40 kDa branched molecule made of two 20 kDa molecules
Positional isomers	4	14
Bond between pegylation and protein chain	Stable amide bond	Unstable urethane bond
Storage	Being stable, can be stored as solution for 2 years	Being unstable, stored as powder form and reconstituted immediately prior to injection
Volume of distribution	8–12 L/kg	1 L/kg
50% absorption	4–5 hrs	50 hrs
Time to peak concentration	20–40 hrs	~80 hrs
Metabolism	70% liver; 30% kidneys	Mainly kidneys
50% elimination	~40 hrs	~65 hrs

adjustment as the free interferon molecule released from PEG-IFN- $\alpha$ 2b is mainly excreted by the kidneys (5). PEG-IFN- $\alpha$ 2b has a wide distribution throughout body fluids and tissues (Table 1) making its weekly dose adjustment based on patient's body weight (1.5  $\mu$ g/kg). In contrast, PEG-IFN- $\alpha$ 2a can be given in a fixed weekly dose of 180  $\mu$ g (6).

So far, recommended treatment of HCV infection is a combination of PEG-IFN- $\alpha$ 2a or - $\alpha$ 2b in their respective doses plus RBV (given based on body weight for genotypes 1 and 4 while fixed dose of 800 mg for genotypes 2 and 3 infections) (7). Treatment is determined to be successful with achievement of a sustained virologic response (SVR) which is defined as being HCV RNA negative after six months of completing the treatment. Achieving SVR is considered the best marker for permanent cure (7). Over the last decade or so, since the discovery of the PEG-IFN, the data on the relative efficacy of PEG-IFN based on its type have been conflicting (8-15). One of the largest study (IDEAL study) in which more

respectively). Data on rapid virological response (RVR) have not been reported in this study (15). Both these studies reported similar types and frequencies of adverse events. Higher efficacy of PEG-IFN- $\alpha$ 2a observed in these two studies, a finding in contrast to what found in the IDEAL study, can be explained by the fact that 40%–50% of patients included in these two studies had genotypes 2 or 3 HCV as compared to only genotype 1 HCV in the IDEAL study.

In this issue of *Hepatitis Monthly*, Alavian *et al.* report a systematic review of several RCTs comparing safety and efficacy of PEG-IFN- $\alpha$ 2a and PEG-IFN- $\alpha$ 2b (16). Authors found that PEG-IFN- $\alpha$ 2a is better and more effective than PEG-IFN- $\alpha$ 2b in terms of achieving the EoT response and SVR. Although, the rate of neutropenia was higher with the PEG-IFN- $\alpha$ 2a as compared to PEG-IFN- $\alpha$ -2b, proportion of patients requiring dose modification or drug withdrawal was similar with the two types of PEG-IFN administered (16). Similar results have also been reported by another meta-analysis (17) (Table 2).

**Table 2.** Meta-analyses of the controlled randomized clinical trials comparing safety and efficacy of Peginterferon- $\alpha$ 2a and Peginterferon- $\alpha$ 2b plus ribavirin in the treatment of hepatitis C virus infection.

	No. of RCTs	No. of patients	RVR	EoT response	SVR	Adverse events	Dose discontinuation
Alavian <i>et al.</i> (16)	7	3,518	Not reported	1.67 (1.24–2.24)	1.38 (1.02–1.88)	1.50 (1.25–1.79) for neutropenia	0.78 (0.47–1.29)
Awad <i>et al.</i> (17)	8	4,335	Not reported	Not reported	1.11 (1.04–1.19)	Not reported	0.79 (0.51–1.23)

RCT: randomized controlled trial; RVR: rapid virological response; EoT: end of treatment; SVR: sustained virologic response

than 3,000 patients infected with genotype 1 HCV infection were randomized into three treatment arms of either PEG-IFN- $\alpha$ 2b 1.0  $\mu$ g/kg/wk, PEG-IFN- $\alpha$ 2b 1.5  $\mu$ g/kg/wk or PEG-IFN- $\alpha$ 2a 180  $\mu$ g/kg/wk (11). Although the end of treatment (EoT) response rate was higher with PEG-IFN- $\alpha$ 2a as compared to PEG-IFN- $\alpha$ 2b (64% vs. 53%), SVR was similar (41% vs. 40%). This was mainly due to higher relapse rate in those treated with PEG-IFN- $\alpha$ 2a as compared to PEG-IFN- $\alpha$ 2b (28% vs. 20%) (11). Recently, two investigators in randomized controlled trials (RCTs) have shown better results with PEG-IFN- $\alpha$ 2a as compared to PEG-IFN- $\alpha$ 2b (14, 15). Rumi *et al.*, randomized 447 patients into either PEG-IFN- $\alpha$ 2a (n=223) or PEG-IFN- $\alpha$ 2b (n=224); both groups also received RBV. Data on rapid virologic response (HCV RNA negative at wk 4), EoT response, and SVR were significantly higher with PEG-IFN- $\alpha$ 2a than PEG-IFN- $\alpha$ 2b (62% vs. 57%; 78% vs. 67%, and 66% vs. 54%, respectively) (14). Another RCT by Ascione *et al.*, also showed better efficacy with PEG-IFN- $\alpha$ 2a (n=160) as compared to PEG-IFN- $\alpha$ 2b (n=160). EoT response and SVR were in favor of PEG-IFN- $\alpha$ 2a (84% vs. 64% and 69% vs. 54%,

What can be the reasons for this selective advantage with PEG-IFN- $\alpha$ 2a? Stability of PEG-IFN- $\alpha$ 2a with its resistance to hydrolysis makes its absorption as well as elimination slower than PEG-IFN- $\alpha$ 2b (18). These pharmacological differences may explain the availability of PEG-IFN- $\alpha$ 2a for a longer period after injection as compared to PEG-IFN- $\alpha$ 2b. Pharmacodynamic studies have shown that PEG-IFN- $\alpha$ 2a is available at a maximum concentration for up to 168 hrs after injection as compared to only 72 hrs for PEG-IFN- $\alpha$ 2b (8, 18).

Demonstration of higher efficacy of PEG-IFN- $\alpha$ 2a in comparison to PEG-IFN- $\alpha$ 2b is another milestone in the evolution of treatment of HCV infection. Better SVR is likely to result in an improved outcome and long-term morbidity and mortality from HCV infection (19). However, further studies comparing the two types of PEG-IFN with longer follow-up are needed to answer this question. Moreover, whether similar efficacy of PEG-IFN- $\alpha$ 2a also applies to special populations such as children, non-responders to initial treatment, and those with HIV co-infection needs to be addressed in future studies (20).

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