THERAPY UPDATE

New developments in the treatment of hepatitis C

S J Rossi, T L Wright

Treatment of chronic hepatitis C virus (HCV) infection with interferon based therapies has been part of clinical practice for more than 10 years. While there have been incremental steps in improving sustained virological response (SVR), limited progress has been made in developing agents that eradicate the virus in all infected patients.¹ The development of effective antiviral agents has been hindered by several key factors, including the genetic heterogeneity of HCV, lack of available culture systems or animal models, limited understanding of the mechanisms of action of current therapies, and the long delay between initiation of therapy and determination of virological response (48–72 weeks). Despite these limitations, progress has been made. The addition of oral ribavirin to standard interferon alfa-2b improved SVR for interferon monotherapy from 9% to 29% for genotype 1, and from 31% to 65% for genotypes 2–3. Peginterferons are the most recent additions to antiviral regimens and two molecules have been approved for the treatment of HCV as monotherapy and in combination with ribavirin.

The process of pegylation involves linkage of interferon to repeating units of non-toxic polyethylene glycol (PEG). The size and linkage of the PEG determines many pharmacological and pharmacokinetic properties of the compound. Peginterferon alfa-2b utilises a 12 kDa PEG linked with a non-covalent bond. This PEG size results in more rapid subcutaneous absorption, wider volume of distribution, and predominantly renal clearance compared with larger molecules.² The non-covalent bond is partially unstable and releases standard interferon, similar to a pro-drug. These properties have resulted in the product being a lyophilised powder and dosing by body weight. Peginterferon alfa-2a utilises a larger 40 kDa PEG molecule covalently bound to interferon alfa-2a. The larger PEG results in slower absorption, primarily intravascular and organ distribution, and largely hepatic clearance compared with the 12 kDa PEG.³ The larger PEG is available in solution and is dosed independent of body weight. Both peginterferons have reduced overall clearance compared

with standard interferon alfa and can be safely administered once weekly.^{2,3} Clinical efficacy of peginterferon alfa as monotherapy^{4–6} and in combination with ribavirin^{7–9} has been evaluated in several large trials (see table 1).

Three studies have evaluated peginterferon versus standard interferon monotherapy in treatment naïve patients.^{4–6} Regardless of the compound studied, peginterferon resulted in higher SVR in both cirrhotic and non-cirrhotic patients. Furthermore, histological improvement was demonstrated even in patients without an SVR, suggesting a therapeutic benefit independent of antiviral activity. However, response remained relatively low for genotype 1 patients and none of the observed SVRs were equivalent to interferon alfa-2b plus ribavirin therapy. Therefore, peginterferon monotherapy is only appropriate for patients in whom ribavirin is contraindicated or in whom it is not tolerated.

There have been three large prospective randomised controlled trials of peginterferon in combination with ribavirin.^{7–9} In two of these trials, standard interferon plus ribavirin was used as the comparator.^{7,8} In combination with ribavirin, peginterferon improved overall SVR compared with that observed with standard interferon by 7% and 9% with peginterferon alfa 2b⁷ and peginterferon alfa 2a,⁸ respectively. For both pegylated products, response was improved in patients with genotype 1 infection but the improvement over standard interferon was modest (table 1). For subpopulations of patients that are the most difficult to treat (those with genotype 1 and high viral load and those with cirrhosis or transition to cirrhosis), again the benefits of combination therapy with peginterferon

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Gastroenterology Section and the Department of Medicine, Veterans Administration Medical Center, University of California, San Francisco, USA
Correspondence to: Dr T L Wright, Gastroenterology Section 111B, VAMC, 4150 Clement St, San Francisco, CA 94121, USA; twright@itsa.ucsf.edu

Table 1 Sustained virological response rates in the phase III peginterferon (PEG IFN) pivotal trials

Interferon	Ribavirin dose	Overall response (%)	Genotype 1 (%)	Genotype non-1 (%)	Genotype 1 + high viral load (%)	Stage 3–4 fibrosis (%)
Lindsay ⁴						
PEG IFN α -2b 1.0 μ g/kg q wk	Not applicable	25	14	47	8	Not available
IFN α -2b 3 MIU TIW	Not applicable	12	6	28	2	Not available
Zeuzem ⁵						
PEG IFN α -2a 180 μ g	Not applicable	39	28	57	14	32
IFN α -2a 6/3 MIU TIW	Not applicable	19	7	40	1	7
Heathcote ⁶ (cirrhosis or transition to cirrhosis)						
PEG IFN α -2a 180 μ g	Not applicable	30	12	51	10	30
IFN α -2a 6/3 MIU TIW	Not applicable	8	2	15	4	8
Manns ⁷						
PEG IFN α -2b 1.5 μ g/kg q wk	800 mg QD	54	42	75	30*	44
IFN α -2b 3 MIU TIW	1000–1200 mg QD	47	33	73	29*	41
Fried ⁸						
PEG IFN α -2a 180 μ g	1000–1200 mg QD	56	46	76	42	43
IFN α -2a 3 MIU TIW	1000–1200 mg QD	45	37	61	33	33

*Data from the Peg-Intron product insert.

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over standard interferon were modest,⁸ or were non-existent⁷ (table 1). One criticism of the pivotal trial of peginterferon alfa 2b has been that the dose of ribavirin used in the combination with peginterferon may have been inadequate.⁷ A retrospective analysis of this study suggested that dosing ribavirin as a function of body weight may result in improved response but this approach has yet to be tested prospectively.⁷ While we do not yet have information about the optimal dose of ribavirin to be used with this product, we have data from a recent trial of peginterferon alfa 2a that treatment of patients with genotype 1 infection is better when administered in combination with 1000/1200 mg of ribavirin (based on a body weight of 75 kg) than with 800 mg.⁹ Moreover, SVR is greater in patients with this genotype when treatment is administered for 48 rather than 24 weeks.⁹ In contrast, 800 mg/day ribavirin in combination with peginterferon alfa 2a (180 µg/week) for 24 weeks is sufficient for patients with genotype non-1 infection.⁹ Whether these recommendations can also be applied with confidence to treatment with peginterferon alfa 2b plus ribavirin remains to be determined.

In combination with ribavirin, the safety profiles of the two pegylated products versus standard interferon can be inferred from the pivotal phase III trials.^{7,8} Incidence of side effects, particularly of injection site reactions, fever, and dose reductions for neutropenia appeared to be greater for peginterferon alfa 2b than for standard interferon.⁷ Incidence of side effects with peginterferon alfa 2a, other than dose reductions for thrombocytopenia, appeared if anything to be less than with standard interferon.⁸ Final recommendations about optimal management of "standard" treatment naïve patients with hepatitis C should await full analysis and peer reviewed publication of these trials.⁹

There are in addition populations in whom there are insufficient data to make recommendations: those who have previously failed standard interferon plus ribavirin, those who have undergone liver transplantation, those with renal insufficiency, those with hepatic decompensation, and those with HCV/HIV coinfection. Data to guide us in the management of these patients are eagerly awaited.

Novel immunomodulatory and direct antiviral therapies are under development.¹⁰ Potential antiviral targets include those involved with processing the viral polypeptide (NS2/3 and NS3/4A protease), viral RNA replication (NS3 helicase, NS5B polymerase), and viral RNA regulation (5' UTR IRES, 3' UTR). Several agents are currently being tested in

humans. Ribavirin analogues (viramidine, levovirin), histamine analogues, and IMPDH inhibitors are in development. Large molecule inhibitors of replication such as ribozymes and antisense oligonucleotides have been tested but their usefulness appears to be limited by their size and toxicities. The greatest promise lies with the small molecule direct antivirals such as helicase, polymerase, and protease inhibitors. While these represent potential advances in HCV therapy, patient management with these agents will likely be complicated by viral resistance, drug toxicity, and drug interactions.

Despite these recent advances, many patients are not suitable treatment candidates due to contraindications to current therapies, and the majority will not respond to available regimens. Future therapies will need to focus on improved efficacy and reduced dose limiting adverse effects. Additionally, appropriate patient selection and pharmacoeconomics of various regimens need to be a primary consideration, given the slow and variable natural history of this disease.

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