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Advances in treatment of chronic hepatitis C: 'Pegylated' interferons

ABSTRACT

New regimens consisting of pegylated interferons plus ribavirin may produce a sustained virologic response in more than 50% of cases of chronic hepatitis C. In contrast, the combination of standard interferon alfa and ribavirin, which was the standard of care until recently, produced a sustained virologic response in 35% to 40% of cases. As the efficacy of newer regimens improves, additional steps to adequately manage their side effects and maximize adherence may become crucial.

KEY POINTS

Formulations of pegylated interferon alfa have half-lives approximately 10 times longer than their standard counterparts and therefore can be given by weekly injections; in contrast, standard interferon alfa must be given by injection three times a week.

Rates of response are lower with any regimen if the virus is of genotype 1 and if the viral load is high.

The treatment may work best if patients receive at least 80% of the interferon dose and 80% of the ribavirin dose, for 80% of the duration of therapy.

Pegylated interferon alfa-2b (Peg-Intron) has been approved by the US Food and Drug Administration (FDA); pegylated interferon alfa-2a (Pegasys) is undergoing FDA review.

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NEW FORMULATIONS of interferon alfa that incorporate polyethylene glycol in the drug molecule are an important advance in the treatment of chronic hepatitis C.

The advantages are several. The new formulations have longer half-lives than the standard formulations and therefore have more steady serum concentrations. They can be given once-weekly instead of three times a week, leading to better compliance. Most important, rates of response and viral eradication are higher.

HEPATITIS C: COMMON AND SERIOUS

Hepatitis C is common: an estimated 4 million Americans and 175 million people worldwide carry the antibody against the hepatitis C virus.[1–2]

The disease has serious consequences. From 75% to 80% of patients exposed to the hepatitis C virus develop chronic hepatitis, 20% to 25% progress to cirrhosis,[3–5] and an estimated 8,000 to 10,000 people each year in the United States die of the complications of hepatitis C-related cirrhosis.[1–5]

Hepatitis C also is a risk factor for hepatocellular carcinoma. People with chronic hepatitis C infection but without cirrhosis have a lifetime risk of hepatocellular carcinoma of 1% to 4%; if they do have cirrhosis, the risk increases to 1% to 4% per year.[6]

Owing to this tremendous disease burden, hepatitis C is currently the most common indication for orthotopic liver transplantation.

MEASURING SUCCESS

Success in treating hepatitis C can be measured in several ways:

Biochemical response—normalization of serum transaminase levels

Virologic response—clearance of viral RNA from the serum

Histologic response—improvement in the histologic activity or fibrosis or both.[7]

The primary goal of therapy is a sustained virologic response, ie, a virologic response that is sustained for 6 months after the end of treatment. Secondary goals include biochemical improvement, histologic improvement, improvement in quality of life, and prevention of hepatocellular carcinoma.

THE TREATMENT OF THE 1990s: MONOTHERAPY WITH STANDARD INTERFERON ALFA

Interferon alfa, alone or in combination with other antiviral agents, was the mainstay of therapy for chronic hepatitis C virus infection in the 1990s.[8]

However, interferon alfa as monotherapy is not ideal. By itself, a standard course of interferon alfa (3 million units three times a week for 12 to 18 months) will cause liver enzyme levels to return to the normal range and hepatitis C viral RNA to decline to undetectable levels in only about 40% of cases.[9–10] Moreover, 50% to 90% of patients who have an initial response subsequently relapse once interferon alfa is stopped. Repeat treatment with interferon monotherapy has an extremely low response rate: 2% to 4.6%.

Hepatitis C is the most common reason for liver transplantation

A meta-analysis[11] of four randomized trials of interferon alfa for chronic hepatitis C revealed an overall biochemical response rate of 46% and a sustained virologic response rate of 15% to 20%. Higher doses and longer courses of treatment have been tried in an effort to enhance response, with little improvement.[12–13]

On the other hand, several factors have been consistently associated with a favorable response to therapy: a low serum level of hepatitis C RNA at baseline, a viral genotype other than genotype 1 or 4, and absence of cirrhosis.[14]

Side effects of interferon

Interferon alfa has significant side effects.

An influenza-like syndrome consisting of fever, chills, myalgias, and malaise occurs early in treatment in as many as 82% of patients, making it the most common side effect of interferon therapy.

Neuropsychiatric complications such as depression, irritability, and anxiety occur in approximately 20% of patients and are usually manageable with antidepressants.

Bone marrow suppression with granulocytopenia, thrombocytopenia, anemia, and alopecia occur in 5% of patients.

These side effects tend to decrease with continued exposure to the drug and with dose adjustment. Many patients tolerate bedtime dosing better than daytime dosing, especially when pretreated with acetaminophen or nonsteroidal anti-inflammatory drugs.

Contraindications to interferon

Interferon alfa is contraindicated in patients with hepatic decompensation, severe myelosuppression, cardiovascular disease, or preexisting severe psychiatric conditions such as major depression.[15]

COMBINATION THERAPY: INTERFERON ALFA AND RIBAVIRIN

The rate of sustained virologic response is higher if interferon alfa is combined with ribavirin, a nucleoside analogue.[16–19] In a large multicenter clinical trial,[20] the rate of virologic response at 24 weeks was 31% with combination therapy vs 6% with standard interferon alfa monotherapy; at 48 weeks, the rate was 38% with combination therapy vs 13% with monotherapy. More than 60% of patients who relapsed after undergoing monotherapy and subsequently received combination therapy achieved viral eradication.

Rates of histologic response have also been higher with combination therapy than with monotherapy.

However, up to 20% of patients cannot tolerate combination therapy owing to side effects such as anemia, depression, and weight loss.[21]

THE NEXT STEP: PEGYLATED INTERFERONS

The half-life of standard interferon alfa-2a is 3.7 to 8.5 hours, and that of standard interfer-

on alfa-2b is 2 to 3 hours.[22] These drugs, which are given three times a week, therefore have wide fluctuations in their serum concentrations, with high peaks and low troughs. Between doses, serum levels drop to low or even undetectable levels, allowing the virus to replicate, contributing to the development of resistant variants of the virus, and perhaps contributing to the high rate of treatment failure.[23–24]

The half-life is increased by attaching a polyethylene glycol (PEG) moiety to the standard interferon alfa molecule. The resulting "pegylated" complex maintains a sustained serum concentration. Therefore, the drug can be given once a week, which is more convenient than the three-times-a-week schedule required with standard interferon alfa.

In addition, polyethylene glycol is inert, water-soluble, and nontoxic and does not adversely affect the safety profile of the interferon product.[25–26]

Pegylated interferon alfa formulations seem to be more effective than the standard formulations. It is proposed that pegylated interferons, with their long elimination half-lives and steady serum concentrations, may prevent viral rebound between doses and reduce the risk of "escape mutants." Although the theory is attractive, further supporting data are needed.

Pharmacokinetics: The bigger the PEG, the longer the half-life

At present, there are two pegylated formulations of interferon alfa, designated 2b (PegIntron) and 2a (Pegasys; undergoing review but not yet approved by the US Food and Drug Administration). These have a reported elimination half-life 10 times longer than their standard interferon alfa counterparts.[27]

Polyethylene glycol exists in a multitude of molecular weights. Size affects the elimination half-life of interferon: as the molecular weight of the polyethylene glycol increases, the elimination half-life of interferon also increases, but in theory its antiviral activity and the renal clearance may decrease. The polyethylene glycol in pegylated interferon alfa-2b is a straight chain weighing 12 KD; the polyethylene glycol in pegylated interferon alfa-2a is a branched chain weighing 40 KD. The half-life of pegylated interferon alfa-2b is about 54 hours and that of pegylated interferon alfa-2a is about 77 hours.

Pegylated interferons have rates of absorption and volumes of distribution similar to those of their standard interferon counterparts.

Pegylated interferon alfa-2a is primarily cleared by the liver.[28] Similarly, 70% of pegylated interferon alfa-2b is cleared by the liver, and 30% is cleared by the kidneys.[29]

It does not seem necessary to reduce the dose of either pegylated interferon alfa-2b or 2a with renal impairment or cirrhosis.

CLINICAL TRIALS OF PEGYLATED INTERFERON MONOTHERAPY

Clinical trials have shown that pegylated interferons are well tolerated, and their efficacy is approximately twice that of their nonpegylated interferon counterparts. In addition, the laboratory abnormalities and the adverse events associated with pegylated interferons are similar to those of nonpegylated products.[27,30–36]

Lindsay et al[30] reported the results of a multicenter clinical trial in 1,219 previously untreated patients with chronic hepatitis C who received either standard interferon alfa-2b (3 million units three times a week for 48 weeks) or pegylated interferon alfa-2b in one of three weight-based dosages (0.5, 1.0, or 1.5 μg/kg per week for 48 weeks).

The pegylated interferon was significantly more effective than the standard formulation. At the end of treatment, 49% of those treated with 1.5 μg/kg per week of pegylated interferon alfa-2b achieved a response, vs 24% with the standard formulation ($P < .001$). Relapse rates were high, however, with sustained response rates of only 23% vs 12%.

Viral genotype and viral load mattered. Multivariate analysis revealed that patients with hepatitis C virus genotype 2 or 3 who received pegylated interferon alfa-2b had a sustained virologic response rate of 35% to 49% (depending on the dose) vs 10% to 14% with genotype 1—more than three times higher. For patients with genotype 1 and a high viral load, the sustained virologic response rate was 7% with the pegylated prod-

Interferon side effects: flu-like symptoms, depression, bone marrow suppression

uct at the highest dose and 2% with the standard interferon. In contrast, patients with genotype 2 or 3 and a low viral load had a 68% rate of sustained virologic response with 1.5 µg/kg per week of pegylated interferon alfa-2b, compared with 36% with the standard interferon alfa-2b.

The safety profile and tolerability were similar for both formulations.

Zeuzem et al[31] reported the results of another large-scale randomized clinical trial in patients with hepatitis C who received either pegylated interferon alfa-2a (180 µg/week for 48 weeks) or the standard high-dose interferon alfa-2a regimen (6 million units three times a week for 12 weeks followed by 3 million units three times a week for 36 weeks).

The sustained virologic response rate with the pegylated interferon was 39%, vs 19% with the standard interferon (P = .001). Viral genotype, viral load, age, and fibrosis stage were independent predictors of response.

Heathcote et al,[32] in a study in hepatitis C patients with cirrhosis, reported a sustained viral response rate of 30% following 48 weeks of therapy with pegylated interferon alfa-2a (180 µg per week), compared with 8% with standard interferon alfa-2a (P = .001).

Reddy et al[33] recently reported a similar sustained virological response rate (36%) in noncirrhotic patients with chronic hepatitis C treated with 180 µg per week of pegylated interferon alfa-2a for 48 weeks.

Response rates are twice as high with pegylated vs standard interferon

THE FUTURE: PEGYLATED INTERFERON PLUS RIBAVIRIN

To date, the highest reported rates of sustained virologic response have been with the combination of pegylated interferon and ribavirin.[34–36]

In a randomized controlled trial,[36] 62% of patients treated with pegylated interferon alfa-2b (1.5 µg/kg per week) in combination with ribavirin had no detectable viral RNA at the end of treatment, and 54% had a sustained virologic response. Patients with hepatitis C genotype 1 had a rate of sustained virologic response of 42%, vs 81% with genotype 2 or 3.

Similar results were reported for the combination of pegylated interferon alfa-2a and ribavirin, with an overall sustained viral response rate of 46% for genotype 1 vs 76% for genotypes 2 and 3.[35]

Although no new predictors of response to pegylated products have been identified, previously important factors (genotype, baseline viral RNA level) remained important.

The combination of interferon alfa-2b plus ribavirin was recently approved by the US Food and Drug Administration and is expected to become widely available.

IMPORTANCE OF ADHERENCE AND OPTIMAL DOSING

In a reanalysis of the initial trials of interferon alfa-2b and ribavirin in combination and the more recent trials of pegylated interferon alfa-2b and ribavirin, McHutchinson[37] noted that improved efficacy can be achieved by delivering at least:

- 80% of the interferon dose, and
- 80% of the ribavirin dose, for at least
- 80% of the standard 48-week duration of therapy.

This so-called 80-80-80 rule underscores the importance of managing side effects and maximizing adherence to the regimen.

Additionally, even greater improvements in the efficacy of these regimens of pegylated interferon alfa-2b and ribavirin are noted with weight-based dosing. In fact, patients who received 1.5 mg/kg per week of pegylated interferon alfa-2b in combination with at least 10.6 mg/kg of ribavirin had a sustained virologic response rate of 61%. Forty-eight percent of patients with hepatitis C genotype 1 and 88% of those with genotype 2 achieved a sustained virologic response with this regimen.[36]

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