



The evolving treatment of chronic hepatitis C: Where we stand a decade out

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■ ABSTRACT

The treatment of hepatitis C has evolved rapidly since the identification of the hepatitis C virus (HCV) in 1989. Since the first accepted therapy for HCV infection, recombinant interferon, received marketing approval a little more than a decade ago, it has come to be used in combination with ribavirin for improved rates of sustained virologic response. Recently, pegylated versions of interferon have been developed for use with ribavirin, offering pharmacokinetic advantages and further improvements in response rates over conventional interferon. This article briefly reviews how these evolving regimens for HCV infection have addressed the subtle and singular characteristics of this challenging virus.

Effective treatment for infection with the hepatitis C virus (HCV) was first described more than a decade ago and has evolved rapidly since. However, to understand the evolution of treatment for hepatitis C, we must look back much further. Critical milestones that cleared the way for the development of management and treatment strategies for hepatitis C include:

- The recognition that different hepatitis viruses exist, and their subsequent identification and characterization
- Growth in knowledge of the mechanisms by which

viruses, and particularly HCV, replicate and cause cell injury

- The explosion in drug development technology driven by modern molecular biology techniques and the race to identify antiviral agents with activity against the human immunodeficiency virus (HIV).

This short review surveys key developments in the discovery of HCV and in our evolving treatment approaches to HCV infection.

■ EPIDEMIOLOGY AND IMPACT OF HEPATITIS C

Infection with HCV is a major cause of chronic liver disease worldwide, affecting 175 million people. In the United States, it is estimated that 2.7 to 4 million people are infected with the virus (the former estimate is based on the Third National Health and Nutrition Examination Survey, which excluded several high-risk groups in the population). On average, up to 80% of acutely infected patients go on to develop chronic infection. At least 20% to 25% of these patients will eventually develop cirrhosis and be at risk for its complications. The sequelae of HCV-induced chronic liver disease account for more than 12,000 deaths annually and are the leading indications for liver transplantation in the United States. HCV-related morbidity and mortality are expected to increase markedly over the next 2 decades.¹

■ DISCOVERY AND CHARACTERIZATION OF HCV

The infectious nature of yellow jaundice was recognized in the 8th century AD. Epidemic jaundice was common, and many or most cases were probably due to enteric transmission of what is now known as the hepatitis A virus. Percutaneous transmission of the disease was not recognized until the advent of inoculation for smallpox vaccination in the 1880s, and many reports of jaundice in patients receiving vaccines or injections for diabetes or syphilis followed in the early 20th century. The first association of blood transfusion

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Disclosure: Dr. Saadeh reported that he has no commercial affiliations or interests that pose a potential conflict of interest with this article. Dr. Davis reported that he has received grant or research support from the Roche, SciClone, Otsuka, Gilead, and InterMune corporations.

with the development of hepatitis was reported in 1943. Landmark studies by Krugman and colleagues at the Willowbrook State School in New York established the transmissibility of hepatitis by human plasma and confirmed long-standing clinical observations that both parenteral (“serum hepatitis”) and enteric (“infectious hepatitis”) transmission could occur.²

Frustrating and largely unsuccessful efforts to identify the specific agents responsible for hepatitis continued over several decades. A serologic marker for hepatitis B virus was identified by Blumberg in 1965, but its association with the parenterally transmitted entity known as serum hepatitis was not recognized until 2 years later.² The specific viral agents responsible for hepatitis B and A came to be recognized over the next few years.² These discoveries were landmark breakthroughs, but it was soon apparent that most cases of hepatitis could not be explained by either the hepatitis A or the hepatitis B virus. The entity of “non-A, non-B hepatitis” was formally christened in the mid-1970s.²

An infectious agent was suspected as the cause of this disease entity since it was parenterally transmissible to chimpanzees and humans by blood transfusion, but identification of the agent proved elusive for many years. Bradley and colleagues at the Centers for Disease Control and Prevention characterized the biochemical nature of the infectious agent, but conventional virologic and immunologic techniques of the time failed to isolate it. Working independently, scientists at Chiron Corporation and scientists in Japan used then-recent molecular biology techniques in attempts to isolate what Bradley’s work had suggested might be an RNA virus resembling the Flaviviridae. The identified peptides cross-reacted with sera from patients with non-A, non-B hepatitis and from experimentally infected chimpanzees. Extrapolation from clones with overlapping regions of the viral complementary DNA subsequently allowed investigators to establish the entire viral genome. This breakthrough led to an explosion of research on this viral agent, now designated “hepatitis C virus,” and its disease, now called hepatitis C.³

A virus with vigorous replication

HCV was subsequently characterized as a flavivirus-like RNA virus, as originally suspected, and over time its replicative cycle has been largely characterized, even though HCV has proven difficult to grow efficiently in cell culture and there are no widely available animal models.

The virus replicates at a very high rate, producing

more than 10^{12} viral copies per day, but the viral half-life is short, resulting in rapid turnover.⁴ Moreover, like other RNA viruses, HCV uses the viral error-prone RNA polymerase for replication, which results in the production of innumerable random uncorrectable nucleotide errors and a heterogeneous virus population that promotes genetic evolution. Today, isolates of the virus are distinguished by their genetic relatedness (genotype) as determined by phylogenetic tree analysis. Six major genotypes and more than 100 subtypes have been defined. We now know that these genotypes have subtle differences in replicative and host interactions, and therefore have important therapeutic implications, as discussed below.

■ PATHOGENESIS OF HCV-RELATED LIVER DISEASE

Multiple factors influence the interaction between HCV and the infected host, resulting in an extremely individual and variable disease presentation. Although viral replication is critical in the development of liver disease from HCV infection, the virus does not appear to be directly cytopathic to liver cells under most circumstances. For example, an exception may be the unique and often lethal cytopathic type of liver injury observed in some transplant recipients with extremely high virus levels. Viral factors such as genotype, the presence and diversity of viral quasi-species, and the level of replication appear unrelated to disease severity in most cases. Rather, it appears that host factors, particularly the cellular immune response, influence the course of the disease. Unfortunately, good characterization of the role of the host immune response in the pathogenesis of liver disease has been hampered by the lack of a small animal model or an efficient cell culture model.

■ TREATMENT OF HCV-RELATED LIVER DISEASE

There were only a few forays into treatment of chronic non-A, non-B hepatitis before the identification of HCV in 1989. Corticosteroids were commonly used to treat chronic hepatitis before viral etiologies were recognized. Prednisone often reduced serum aminotransferase levels, but normalization of liver enzyme levels or a significant improvement in disease course was not noted. Acyclovir was studied in a small pilot trial and did not change the aminotransferase levels.

Interferon monotherapy

Interferons were first described in 1957 by Isaacs and Lindeman and were so named because of their ability to “interfere on” viral replication. Interferons are nat-

urally occurring glycoproteins that are produced *in vivo* by leukocytes in response to viral infection. Pharmacologic doses of interferons were first produced by stimulation of cultures of buffy-coat lymphocytes collected from blood donors. Later, interferons were produced commercially from cell lines or the much more efficient recombinant technology. Most commercially available interferons today are recombinantly produced.

Interferons inhibit the replication of many viruses, including hepatitis viruses, through a variety of mechanisms, including direct antiviral action (inhibition of virus attachment and uncoating, induction of intracellular proteins and ribonucleases) and by amplification of specific (cytotoxic T lymphocyte) and nonspecific (natural killer cell) immune responses.⁵ Although interferon alfa ("interferon" hereafter) suppresses the level of HCV replication, it is generally believed that HCV clearance is mediated at least in part by enhancement by interferon of the host immune response to the virus.

In the late 1980s, interferons became the first agents to be systematically studied for treatment of what was then called chronic non-A, non-B hepatitis.⁶ Those early studies demonstrated that a 6-month course of recombinant interferon normalized serum alanine aminotransferase (ALT) levels in nearly half of treated patients (47% vs 2% in untreated controls) and reduced hepatic inflammation in most treated patients (67% vs 15% in untreated controls).⁷ When molecular tools later emerged to detect the etiologic agent of the disease, analysis of stored samples showed a loss of detectable HCV RNA in most of the patients who had achieved a biochemical response during treatment.

Unfortunately, responses to the short courses of interferon initially employed were often transient, and relapse was common when treatment was stopped. Sustained normalization of ALT levels was demonstrated in about 20% of cases, and sustained loss of virus occurred in only 8% to 11%.² However, no other treatments were available for patients with chronic hepatitis C. Thus, despite the meager rate of permanent viral and biochemical response to a 6-month course of therapy, recombinant interferon was approved by the US Food and Drug Administration in 1991.

Extending the treatment course from 6 to 12 months did not improve the proportion of patients with normalization of serum ALT, but fewer patients relapsed after treatment was stopped, so that sustained improvement was achieved in 38% of patients given a 12-month course compared with 22% of those given a 6-month course.⁷ Sustained loss of virus persisting for

at least 6 months after completion of therapy, hereafter referred to as sustained virologic response (SVR), was observed in up to 30% of cases, but averaged about 16%.^{2,8} Furthermore, histologic improvement was seen in most patients treated for 1 year. Other regimen variations, including daily dosing, escalating doses, and high-dose induction therapy, were also studied, but these did not increase response rates compared with conventional three-times-weekly interferon monotherapy. Furthermore, higher-dose regimens were poorly tolerated.

Ribavirin monotherapy

Ribavirin is a nucleoside analog with a structure similar to azathioprine. It has been known for 30 years to have antiviral activity against several viruses. Ribavirin is well absorbed in the proximal small intestine and, upon entering cells, is phosphorylated to ribavirin triphosphate, which impedes transportation across cell membranes unless it can be dephosphorylated. At an oral dosage of 600 mg twice daily, steady state is reached after approximately 4 weeks.

Ribavirin's mechanism of action against HCV is not known. Early studies using oral ribavirin monotherapy, given at a dosage of 600 mg twice daily, found that serum ALT levels fell to within the normal range in 40% of treated patients, and this was associated with a reduction in hepatic inflammation.⁹ Moreover, fatigue improved despite the hemolytic anemia and the mean fall in hemoglobin of more than 2 g/dL that occurred with treatment. Virus levels, however, did not change during treatment.⁹ Although these studies did not demonstrate antiviral efficacy, the results were intriguing enough to encourage further investigation, including use in combination with interferon.

Combination therapy with interferon and ribavirin

The combination of oral ribavirin with recombinant interferon given three times per week led to significant improvement in the SVR rate compared with interferon alone. Reports from studies of treatment-naïve patients demonstrated SVR rates of 30% after 24 weeks of combination therapy compared with 6% after 24 weeks of interferon monotherapy.^{8,10} A 48-week treatment course achieved SVR in 38% of treatment-naïve patients receiving combination therapy, compared with 13% of those receiving interferon monotherapy.⁸ The benefit of extending therapy to 48 weeks was confined to patients infected with HCV genotype 1; in these patients, the SVR rate was 28% with 48 weeks of therapy vs 16% with 24 weeks. Extending therapy conferred no benefit in patients

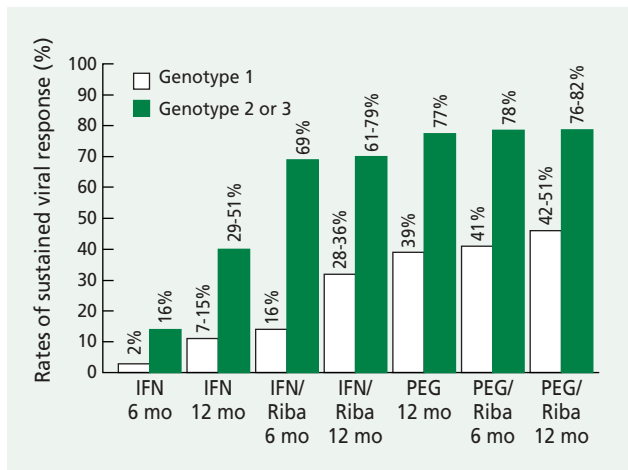


FIGURE 1. Rates of sustained virologic response, presented by patients' HCV genotype, to various interferon-based regimens over the last 15 years (IFN = interferon; PEG = pegylated interferon; Riba = ribavirin). Rates presented as ranges represent data from more than one trial (bar heights represent the mean of the range in these cases).

with genotypes 2 or 3 (SVR of 66% with 48 weeks vs 69% with 24 weeks).

Combination therapy was also beneficial in patients who had a suboptimal response to interferon alone. In one major trial, patients who relapsed following interferon monotherapy achieved higher SVR rates when retreated with combination therapy than with interferon monotherapy (49% vs 5%).¹¹ Additionally, SVR has been achieved in 10% to 25% of nonresponders to IFN monotherapy who have been retreated with combination therapy.¹²

The FDA approved the combination of oral ribavirin and interferon in 1998 for the treatment of patients with chronic HCV infection who relapsed within 1 year of initial therapy. Data showing clear improvement of outcomes in treatment-naïve patients led to extension of the indication later that year to include previously untreated patients as well.

Pegylated interferons

One reason for the limited response to interferon is its short half-life (2 to 5 hours), which leads to wide fluctuations in plasma concentrations of the drug during treatment. Given the vigorous replication kinetics of HCV described above, it was expected that intermittent dosing of interferon would not be optimal for viral suppression.

Pegylation of interferon, in which polyethylene glycol (PEG) is covalently attached to the parent drug, reduces renal clearance, prolongs the plasma half-life, and increases drug exposure over time, per-

mitting once-weekly dosing. Two pegylated interferon products—peginterferon alfa-2a and peginterferon alfa-2b—are now commercially available for human use. Despite differences in the pharmacokinetic properties of these two pegylated compounds, both are dosed once weekly, with drug levels still detectable before the next dose, and they are associated with similar treatment responses.

Combination of pegylated interferon and ribavirin

The combination of pegylated interferon and ribavirin is easier for patients to use, improves SVR in most groups of previously untreated patients, and is the current standard of care for patients with chronic hepatitis C.

Two clinical studies compared 1 year of therapy with either pegylated interferon and ribavirin or nonpegylated interferon and ribavirin.^{13,14} Despite differences between these trials in study design, the pegylated interferon agents used, the ribavirin doses used, and patient characteristics, the outcomes were remarkably similar: SVR was achieved in 54% to 56% of treated patients (41% to 42% for patients with genotype 1 and 66% to 75% for those with genotype 2 or 3).

Optimal treatment durations and ribavirin doses have recently been more clearly defined for these combination regimens. For patients with HCV genotype 1, the optimal course is 1 year of therapy with pegylated interferon plus ribavirin given at a dosage of 1,000 mg/d for those with body weight less than 75 kg and 1,200 mg/d for those weighing more than 75 kg.¹⁵ However, for patients with HCV genotype 2 or 3, response is just as good with only 6 months of combination therapy with pegylated interferon and ribavirin 800 mg/d as it is with a longer treatment course and higher ribavirin doses. Thus, determining the viral genotype before treatment remains a critical step in selecting the best treatment regimen.

Optimal dosing and treatment duration with this combination regimen are discussed in greater detail in the next article in this supplement.

Clinical benefits of sustained virologic response

Sustained virologic response to interferon-based treatment is durable, with late relapse or reinfection occurring in only about 3% of responders.¹⁶ SVR is further associated with a reduction of hepatic inflammation on liver biopsy, often to normal, and stabilization of hepatic fibrosis, with actual regression in more than half of cases.¹⁷ It is reasonable to assume that these short-term benefits translate into a reduction in

morbidity and mortality. In addition, response to therapy is associated with an improvement in health-related quality of life.

■ THE NEXT 10 YEARS: REMAINING CHALLENGES

Over the last decade, our knowledge and treatment of chronic hepatitis C have evolved considerably. SVR remains the goal of treatment, as it connotes durable virus eradication, histologic improvement, and improved quality of life. While initial treatment, consisting of nonpegylated interferon alone for 6 months, was associated with disappointing SVR rates of less than 10%, the current standard of care, pegylated interferon plus ribavirin, is associated with HCV eradication in more than half of treated patients (Figure 1).

Despite our remarkable progress, several obstacles to improving treatment results remain. As detailed later in this supplement, many patients are unable to begin or tolerate interferon-based therapy because of medical contraindications, cytopenia, or neuropsychiatric symptoms. Other groups respond less well to treatment, including those with genotype 1 and high virus levels, coinfection with HIV or hepatitis B virus, advanced hepatic decompensation, obesity, or African American ethnicity. Clearly, there is considerable room for improvement in our treatment options. More tolerable therapeutic regimens must be found and antiviral agents that target the replicative machinery of the virus must be identified as a way to treat patients who cannot receive or tolerate interferon-based regimens.

■ REFERENCES

1. Davis GL, Albright JE, Cook SE, et al. Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl* 2003; 9:331–338.
2. Davis GL. Hepatitis C. In: Schiff ER, Maddrey W, Sorrell M, eds. *Schiff's Diseases of the Liver*. 9th ed, vol. 1. Philadelphia: Lippincott Williams & Wilkins; 2002:807–861.
3. Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989; 244:359–362.
4. Neumann AU, Lam NP, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon- α therapy. *Science* 1998; 282:103–107.
5. Peters M, Davis GL, Dooley JS, et al. The interferon system in acute and chronic viral hepatitis. In: Popper H, Schaffner F, eds. *Progress in Liver Diseases*, vol. 8. New York: Grune and Stratton; 1986:453–467.
6. Davis GL, Balart LA, Schiff ER, et al. Treatment of chronic hepatitis C with recombinant interferon α . A multicenter randomized, controlled study. *N Engl J Med* 1989; 321:1501–1506.
7. Poynard T, Leroy V, Cohard M, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. *Hepatology* 1996; 24:778–789.
8. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon α -2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 1998; 339:1485–1492.
9. Bodenheimer HC, Lindsay KL, Davis GL, et al. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. *Hepatology* 1997; 26:473–477.
10. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon α 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon α 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998; 352:1426–1432.
11. Davis GL, Esteban-Mur R, Rustgi V, et al. Interferon α -2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. *New Engl J Med* 1998; 339:1493–1499.
12. Shiffman ML. Management of interferon therapy nonresponders. *Clin Liver Dis* 2001; 5:1025–1043.
13. Manns MP, McHutchison JG, Gordon S, et al. Peginterferon α -2b plus ribavirin compared to interferon α -2b plus ribavirin for the treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358:958–965.
14. Fried MW, Shiffman ML, Reddy R, et al. Peginterferon α -2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347:975–982.
15. Hadziyannis SJ, Cheinquer H, Morgan T, et al. Peginterferon α -2a (40 KD) (Pegasys) in combination with ribavirin: efficacy and safety results from a phase III, randomized, double-blind, multicentre study examining the effect of duration of treatment and ribavirin dose. *J Hepatol* 2002; 37(suppl):536A. Abstract.
16. McHutchison J, Davis GL, Esteban-Mur R, et al. Durability of sustained virologic response in patients with chronic hepatitis C after treatment with interferon α -2b alone or in combination with ribavirin. *Hepatology* 2001; 34(4 Pt 2):244A. Abstract.
17. Shiratori Y, Imazeki F, Moriyama M, et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Intern Med* 2000; 132:517–524.