

Future Treatment Options in Hepatitis C Virus Infection

a report by

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Approximately 170 million individuals are infected with hepatitis C virus (HCV) worldwide, that is, 3% of the world population. Chronic HCV infection is responsible for substantial liver-related morbidity and mortality, related to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Industrialized areas of the world face a high prevalence of infection, ranging from 0.5% to 2.5%. Approximately four million Americans and nine million Europeans are chronic HCV carriers, and HCV has become the leading indication for liver transplantation in these areas. The main objective of antiviral therapy is the cure of chronic HCV infection, which prevents evolution towards severe complications of chronic liver disease. Current therapy is based on the combination of pegylated interferon (peginterferon) alpha and ribavirin. A large number of potentially novel therapeutic options are currently at the developmental stage. They are expected to further increase the cure rate, but raise several issues among which efficacy, tolerance, and resistance appear as the most important.

The standard treatment of chronic hepatitis C is the combination of peginterferon and ribavirin. Both the dose of ribavirin and treatment duration must be tailored to the HCV genotype. Patients infected with HCV genotypes 2 and 3 must be treated for 24 weeks with a low dose of ribavirin (0.8g qd), whereas patients

infected with HCV genotypes 1, 4, 5, and 6 must be treated for 48 weeks with a higher dose of ribavirin (1.0-1.2g qd, according to body weight).¹ Stopping rules based on HCV RNA load monitoring have been derived in patients infected with HCV genotype 1, allowing them to stop therapy at week 12 or 24 when they have virtually no chance of achieving a definitive clearance of infection.¹

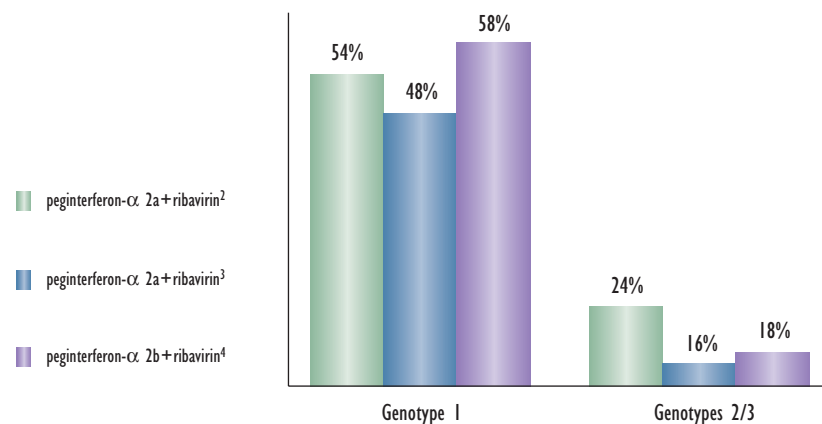
The results of three large-scale pivotal trials²⁻⁴ have shown that, using standard schedules of peginterferon-ribavirin combination, 16% to 24% of HCV genotypes 2- and 3-infected patients, and 48% to 58% of HCV genotype 1-infected patients failed to eradicate infection (see *Figure 1*). These failure rates were shown to be higher in patients coinfecting with HCV and human immunodeficiency virus.⁵⁻⁷ Such virological failure of therapy appears to be multifactorial, as a result of the treatment schedule, host factors, disease-related characteristics, and viral factors.⁸ Full adherence to therapy as well as the administered dose of ribavirin per body weight is crucial, and underdosing, related to inadequate tailoring to body weight or dose reductions caused by the occurrence of severe hemolytic anemia, results in an increased relapse rate during and after therapy. Patient characteristics, such as older age, male gender, high body weight, or race, are also associated



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Figure 1: Rate of Virological Failure (Failure to Definitively Eradicate HCV Infection) According to the HCV Genotype in Three Multicenter Randomized Trials where HCV-infected Patients were Treated with Standard Doses of Peginterferon Alpha and Ribavirin²⁻⁴



with lower rates of viral clearance. Patients with advanced fibrosis or cirrhosis more often fail to eradicate infection upon therapy. Finally, viral factors are involved in the failure of peginterferon-ribavirin treatment to eradicate infection, although the underlying mechanisms remain unclear.^{7,8}

Today, physicians have virtually nothing to offer to patients who failed to eradicate infection during peginterferon-ribavirin therapy. Although a substantial number of these patients have mild-to-moderate disease and can be followed for several years awaiting novel therapeutic options to be available, others are particularly problematic because of evolving liver disease that may rapidly lead to end-stage liver disease or hepatocellular carcinoma. The limitations of current HCV therapy thus justify the urgent need for novel therapeutic options.

Future Treatment Options

Novel directions in HCV therapy are aimed at increasing the cure rate. Only patients who would be intrinsically unable to ultimately cure infection, perhaps for immunological reasons, could eventually benefit from 'suppressive' therapy maintaining low-level viral replication without clearance, in order to slow the progression of liver disease. Complementary approaches based on anti-fibrotic strategies could also be helpful in such patients. This article focuses on novel antiviral strategies. Schematically, novel HCV therapeutic options can be classified into four categories:

- new interferons;
- alternatives to ribavirin;
- specific HCV inhibitors; and
- immune therapies.⁹

The intrinsic antiviral properties of interferon alpha can be increased by modifying the amino acid sequence, for instance, by using a consensus interferon alpha sequence, or by gene shuffling the family of different human interferon alpha DNA encoding sequences. These molecules, as well as interferon beta (another type I interferon), can be pegylated – i.e. combined with various forms of polyethylene glycol molecules – in order to improve their pharmacologic properties. Alternatives to pegylation exist, such as fusion of interferon alpha with human serum albumin. The role of additional naturally occurring interferon species such as interferon gamma or omega alone or in combination with interferon alpha is also being studied.⁹

Ribavirin significantly enhances the sustained viral clearance rate when combined with interferon alpha, but the underlying mechanisms remain unknown. However, hemolytic anemia is a frequent side effect that limits ribavirin dosing, thus decreasing combination efficacy. The development of alternatives to ribavirin that would mimic its beneficial effects with a much better tolerance profile therefore appears as a good means to improve the results of peginterferon alpha combination therapy. Various approaches have been studied. Inhibitors of the inosine monophosphate dehydrogenase (IMPDH) showed no or minimal efficacy. Similarly, clinical trials using levovirin, the L-sugar analogue of ribavirin, in combination with peginterferon alpha have been stopped early because of poorer antiviral efficacy than ribavirin. Viramidine, the amidine version of ribavirin, which is converted by adenosine deaminase to ribavirin preferentially in the liver,¹⁰ currently remains the only promising candidate. Interim analysis of an on-going clinical trial showed a lower hemoglobin drop than with conventional combination therapy. If viramidin's antiviral efficacy happens to be of the same order as that of ribavirin, there is little doubt that viramidin will replace ribavirin in standard combination therapy.

Another exciting approach is the use of specific antiviral molecules that target functional viral components, including viral RNA structures and enzymes.⁹ These molecules are virustatic and significantly reduce viral replication. However, they are not sufficient to achieve a sustained viral clearance, that needs infected cells to be

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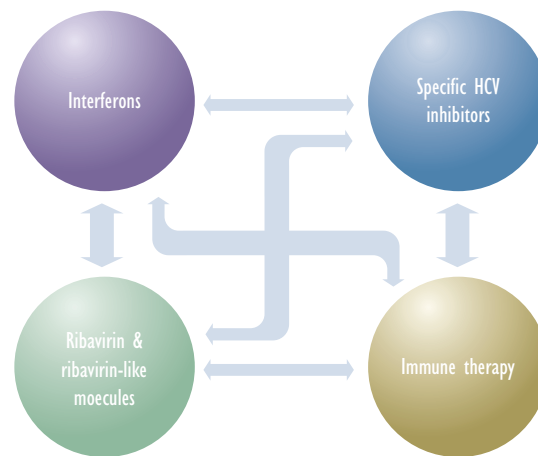
progressively cleared by the immune system in the context of viral production reduction. Nucleic acid-based therapy, including antisense oligonucleotides, ribozymes, and silencing RNAs, has shown promising *in vitro* results, but its application in clinics has been disappointing. Most current approaches target the three-dimensional (3-D) functional structures of HCV RNA (such as the internal ribosome entry site) and proteins. Among the various HCV proteins, the two most obvious targets are the HCV NS3 proteinase and the NS5B RNA-dependent RNA polymerase (RdRp). A number of peptide-based or peptidomimetic inhibitors have been developed to inhibit the NS3 serine proteinase, such as substrate analogs, serine-trap inhibitors (or transition-state analogs), and product analogs. Efforts to discover non-peptide inhibitors are also being made. Recently, the concept that a specific HCV protease inhibitor could reduce viral replication by several logs upon two days of administration has been proven,¹¹ opening the way to the clinical development of such inhibitors. Specific inhibitors of HCV RdRp are also being developed, including both nucleoside/nucleotide analogs and non-nucleoside inhibitors. Several of these drugs recently entered or will soon enter clinical evaluation.

The last potential new direction in HCV therapy is immune therapy that aims at modulating the host immune response to infection. Oral interferon inducers have been suggested to be of potential interest, awaiting clinical proof of concept. Hyperimmune HCV immunoglobulins were shown to bear some protective properties *in vitro* and in experimentally infected chimpanzees. Clinical trials are underway to determine whether they could be used to prevent reinfection of liver grafts after liver transplantation. Finally, various therapeutic vaccine strategies are currently being studied,¹² but the proof of the concept that therapeutic vaccination could be beneficial in chronic HCV still remains to be made.

Expected Issues

The development of a new drug, a new class of drugs, or a new therapeutic strategy faces a number of issues. This is particularly the case in chronic HCV, where the clinical expectations are high, targeting improvement of the cure rate. There is no doubt that future standard therapy will be based on the combination of different drugs and approaches, although it is so far unclear which combination(s) will provide the best efficacy (see Figure 2). It is likely that first-line treatment will be tailored to individual patient characteristics, and that the treatment schedule will be tailored on-therapy to the virological

Figure 2: Future Classes of Treatment Options in Chronic HCV



The arrows represent potential combinations of different therapeutic approaches. Validated combinations will likely be tailored to the individual patient on the basis of baseline parameters and the early virological response to therapy.

response, as assessed by viral load monitoring. Among the principal questions is that of the future of interferon and ribavirin or ribavirin-like molecules. Will new therapies replace the current standard of care or add to it? Will ribavirin or ribavirin-like molecules be replaced by novel therapeutic approaches? Will they, on the contrary, still be needed to make the sustained virological response to specific inhibitors that will replace interferon? The answers to all of these questions will come from carefully performed clinical trials where multiple combination options will be studied. However, many steps and obstacles need to be overcome, including demonstration of the clinical efficacy of any new drug in development. Many drugs that were showing promising results *in vitro* have already disappeared from the field due to very disappointing clinical results. Tolerance and toxicity are also major issues. Severe side effects cannot be accepted in the treatment of a slow life-threatening disease such as HCV infection. Again, many promising drugs or classes of drugs have already disappeared from the field because of worrisome preclinical toxicity profiles. Finally, the issue of HCV resistance, which principally applies to specific HCV inhibitors, remains as a Damocles' sword above the head of drug companies developing such molecules. The intrinsic virological properties of HCV, together with what is known about hepatitis B and HIV infections, tell us that resistance will occur, probably often and early during therapy. A major goal in HCV therapy will be to start combination therapies as early as possible to avoid killing new drugs before they can help to kill infection. Let us hope that the mistakes of the past will not be made again in the future. ■

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