

Perspective

Moving Beyond Interferon Alfa: Investigational Drugs for Hepatitis C Virus Infection

Numerous direct-acting drugs to treat hepatitis C virus (HCV) infection are in development, offering the potential for substantial improvement over current interferon alfa–based therapy and the possibility of effective interferon alfa–sparing regimens in achieving cure of HCV infection. Drugs furthest along in clinical development include HCV nonstructural protein 3 (NS3) protease inhibitors (eg, telaprevir, boceprevir), which have potent anti-HCV activity but low barriers to resistance and considerable likelihood of cross-resistance. Nucleoside analogue nonstructural protein 5B (NS5B) polymerase inhibitors exhibit a high barrier to resistance and cross-HCV genotype and subtype activity. Nonnucleoside analogue polymerase inhibitors have a low barrier to resistance and are characterized by a substantial frequency of preexisting resistance mutations. The initial use of direct-acting drugs will be as add-on treatment to interferon alfa and ribavirin regimens. The success of interferon alfa–sparing regimens will depend on presenting a sufficiently high barrier to resistance with direct-acting drugs and whether the immunomodulatory effects of interferon alfa are needed for cure of HCV infection. This article summarizes a presentation by David L. Wyles, MD, at the International AIDS Society–USA continuing medical education program held in San Francisco in May 2010.

The prevalence of hepatitis C virus (HCV) infection–related cirrhosis and end-stage liver disease (ESLD) is expected to peak around 2020, reflecting the gradual course of progression of HCV disease in individuals infected several decades ago during the peak incidence of infection. The burden of HCV infection in HIV-infected patients is substantial. Reports from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study in 2006 and 2009 show that liver-related mortality is the most common non–AIDS-related cause of death in HIV-infected patients (D:A:D Study Group and Smith, *AIDS*, 2010; Weber et al, *Arch Intern Med*, 2006).

Interferon alfa–based therapy for HCV infection and its delivery to patients leave much to be desired. A majority of HCV-infected patients are ineligible for therapy, and a sizeable proportion of eligible patients refuse

treatment. Moreover, a majority of treated patients have no response or discontinue treatment, leaving a very small proportion of the total population of HCV-infected patients with the sustained virologic response (SVR) associated with cure. Limitations of interferon alfa–based therapy include relatively low SVR rates (eg, 40%–45% in HCV genotype 1 infection); markedly lower SVR rates in certain populations (eg, 20% in HIV and HCV coinfection and 20%–25% in blacks even with mono-infection); poor tolerability (including that associated with frequent use of growth factor support), resulting in discontinuation by 10% to 15% of patients for adverse events alone; numerous contraindications; and poor acceptance of therapy.

There is considerable hope that new, direct-acting antiviral drugs and other novel drugs will increase the proportions of HCV-infected patients who can tolerate treatment and patients who achieve cure. Dozens of such drugs are currently in development, notably including nonstructural protein 3 (NS3) protease inhibitors and

nucleoside analogue and nonnucleoside analogue nonstructural protein 5B (NS5B) polymerase inhibitors.

Characteristics of Hepatitis C Virus

HCV is a positive-strand RNA virus featuring several nonstructural proteins that are being targeted for drug development. Host cell factors (eg, cyclophilin A) also play key roles in viral replication, providing additional pharmacologic targets. HCV exhibits extremely wide genetic heterogeneity both within and across genotypes, including a 30% to 40% difference in nucleotide sequences between genotypes. Like the replication rate of hepatitis B virus (HBV) (10^{12-15} virions/day) and HIV (10^{10} virions/day), the replication rate of HCV (10^{12} virions/day) is high, producing approximately 10- to 100-fold more virions per day than HIV.

This high replication rate combined with an error-prone viral polymerase and absence of overlapping reading frames drives the genetic diversity of HCV. This diversity includes production of resistant variants of HCV that can elude the inhibitory effects of antiviral drugs that target components of the viral life cycle. For HCV, transcription errors may be multiplied because there are 2 rounds of transcription (from positive to negative strand RNA, and from negative back to positive strand) that utilize the error-prone NS5B polymerase. Unlike for HBV and HIV infections, eradication of HCV does occur. Infected-cell turnover with HCV is not as rapid as that with HIV and more rapid than that with HBV.

NS3 Protease Inhibitors

The HCV NS3 protease, which is necessary for viral replication, has an exposed active site that has made development of small molecules that tightly

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bind the site difficult. The geometry of the active site also increases the potential for cross-resistance because there are only a limited number of “good” contacts that small molecule inhibitors can make with the binding site. Despite the challenges in design, NS3 protease inhibitors were the first class of direct-acting anti-HCV drugs validated in the clinic and are the furthest along in clinical trials.

When used in combination with standard-dose peginterferon alfa plus ribavirin therapy, NS3 protease inhibitors may increase SVR rates in patients with HCV genotype 1 from 40% to as high as 75%. Randomized phase II trials of telaprevir and boceprevir (investigational drugs in this class that are now in phase III trials) showed SVR rates substantially higher than those achieved with 48 weeks of peginterferon alfa plus ribavirin treatment. In the phase II trials, telaprevir was administered for 12 weeks and peginterferon alfa plus ribavirin for 24 weeks or 48 weeks. Boceprevir was administered with peginterferon alfa plus ribavirin for 28 weeks or 48 weeks (Figure 1). Two additional arms in the boceprevir study looked at a 4-week lead-in with peginterferon alfa and ribavirin, followed by 24 weeks or 44 weeks of triple-combination therapy. The 4-plus-44-week arm had the highest SVR rate at 75% (Hézode et al, *N Engl J Med*, 2009; Kwo et al, *EASL*, 2009; McHutchison et al, *N Engl J Med*, 2009).

Shorter durations of peginterferon alfa plus ribavirin treatment were associated with greater relapse (posttreatment) and, in some cases, lower SVR rates; the omission or use of lower doses of ribavirin was also associated with poorer outcome. Telaprevir was associated with severe rash in 5% to 7% of patients (vs 0%–1% in patients receiving peginterferon alfa plus ribavirin) and an additional decline in hemoglobin level of approximately 0.5 g/dL. Viral breakthrough occurred in 7% to 10% of patients receiving telaprevir; 90% to 95% of patients who experienced breakthrough and 95% of patients who had relapsed had virus with resistance mutations. Boceprevir was associated with anemia in 52% to 63% of patients

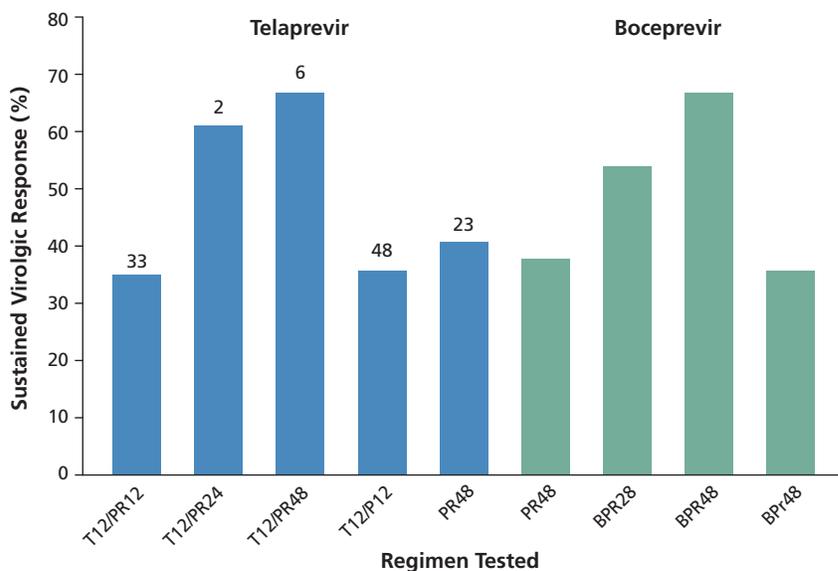


Figure 1. Sustained virologic response rates in phase IIb trials of telaprevir and boceprevir. B indicates boceprevir; P, peginterferon alfa; r, low-dose (400-1000 mg) ribavirin; R, expanded dose (800-1400 mg) ribavirin; T, telaprevir. Numerals in regimens indicate weeks of treatment. Numerals atop bars indicate relapse rate. Based on data from Hézode et al, *N Engl J Med*, 2009; Kwo et al, *EASL*, 2009; McHutchison et al, *N Engl J Med*, 2009.

compared with 34% of patients in the peginterferon alfa plus ribavirin control group and was associated with dysgeusia in 21% to 44% versus 9%, respectively. With both investigational drugs, discontinuation rates were higher in the HCV NS3 protease inhibitor groups than in the control groups.

NS5B Polymerase Inhibitors

There are several sites on NS5B polymerase that can serve as drug targets, including the active site targeted by nucleoside analogue NS5B inhibitors and 2 sites each on the “palm” and “thumb” of the polymerase structure that are targeted by nonnucleoside analogue NS5B inhibitors. Two main categories of nucleoside analogue NS5B polymerase inhibitors exist: (1) compounds that feature a 2'-C-methyl group and (2) compounds with a 4'-azido group. As an example of activity observed with these drugs, the 2'-C-methyl compound R7128 (a prodrug of the nucleoside analogue PSI-6130) was associated with a 2.7 log₁₀ IU/mL reduction in HCV RNA level at 1500 mg twice daily and a 5 log₁₀ IU/mL reduction when administered in combina-

tion with peginterferon alfa plus ribavirin. R7128 was also associated with a rapid virologic response rate of 75% in a phase I evaluation. The drug is now undergoing phase II testing at doses of 1000 mg and 1500 mg twice daily (Lalezari et al, *EASL*, 2008).

A 4'-azido compound, R1626 (a prodrug of the nucleoside analogue R1479), produced a 5.2 log₁₀ IU/mL reduction in HCV RNA level when administered with peginterferon alfa plus ribavirin but was associated with hematologic toxicity that required dose modification in 90% of patients and discontinuation of treatment in 50%; it also resulted in a high relapse rate. Thus, clinical development was halted after the phase II trial (Pockros et al, *Hepatology*, 2008).

The prodrug of a uridine nucleotide analogue, PSI-7851 was developed based on findings that the minor intracellular uridine metabolite of PSI-6130 had a longer half-life and reached substantially higher triphosphate levels in cells than the parent drug. Early-phase testing of PSI-7851 showed that a 400-mg, once-daily dose was associated with a reduction in HCV RNA of approximately 2 log₁₀ IU/mL. PSI-7851,

as well as PSI-7977 (a racemically pure form), continue in phase II evaluation (Rodríguez-Torres et al, AASLD, 2009; Furman et al, AASLD, 2008).

With regard to nonnucleoside analogue NS5B polymerase inhibitors, the 2 palm sites have considerable overlap, increasing the likelihood of cross-resistance among drugs targeting these sites. The rapidity with which resistance can emerge during monotherapy is demonstrated by data on the nonnucleoside analogue HCV-796, a “palm 2” inhibitor. The highest doses of this drug administered alone were associated with reductions in HCV RNA of approximately $1.5 \log_{10}$ IU/mL at day 3, with viral load rising thereafter and approaching baseline by day 14 in association with resistance mutations. Development of this drug was halted in phase II testing because of hepatotoxicity. Other investigational drugs that have advanced to phase II studies include ANA598 (a “palm 1” molecule), which yielded a $2.9 \log_{10}$ IU/mL reduction in viral load at 800 mg twice daily for 4 days in a phase I study and showed cross-resistance to palm 2 compounds, and VCH-222 (a “thumb 2” compound), which produced a $3.7 \log_{10}$ IU/mL reduction at 750 mg twice daily.

Other Targets

Other potential drugs with HCV targets include entry inhibitors and inhibitors of other nonstructural proteins, including nonstructural protein 4A (NS4A; serine protease cofactor), nonstructural protein 4B (NS4B; membrane alterations), and nonstructural protein 5A (NS5A; phosphoprotein). Anti-HCV drugs in development with nonviral targets include cyclophilin inhibitors and thiazolidines (including nitazoxanide, an antiparasitic drug with anti-HCV activity). Antagonists of NS5A, a phosphoprotein essential for viral replication, have shown considerable activity in early evaluation. A phase I study of the investigational NS5A inhibitor BMS-790052 showed a reduction in viral load of approximately $3.5 \log_{10}$ IU/mL that persisted for 1 week after a single 100-mg dose. This

drug is likely suitable for once-daily dosing given that a 1-mg dose (which was associated with a reduction in viral load of approximately $2 \log_{10}$ IU/mL in the phase I study) exhibited a plasma concentration above the 90% effective concentration (EC_{90}) at 24 hours after dosing (Nettles et al, AASLD, 2008).

Resistance

Protease Inhibitor Resistance

Resistance to NS3 protease inhibitors emerges very rapidly in vivo, occurring within 3 days. Less than 1% of viral quasiespecies carry drug resistance mutations before drug exposure; however, these variants are rapidly selected in response to drug pressure (Bartels et al, *J Infect Dis*, 2008). Among the first wave of NS3 protease inhibitors, hallmark resistance mutations that confer cross-resistance are A156V/T and R155K/T substitutions; both loci are within or close to the protease active site. Virus with the R155K/T mutation displays a moderate increase (10-fold–20-fold change) in the median effective concentration (EC_{50}) while retaining replication fitness, whereas virus with the A156V/T mutation displays a large increase (>100-fold change) but has reduced fitness (Sarrazin et al, *Gastroenterology*, 2007).

The HCV subtype impacts drug resistance development. For example, with regard to the R155K resistance mutation, genotype 1a virus requires only 1 nucleotide change, whereas most genotype 1b isolates require a 2-nucleotide change, translating into a higher resistance barrier. To date, essentially all resistance related to the R155K mutation has been observed in patients with the HCV genotype 1a subtype (Hézode et al, *N Engl J Med*, 2009; McHutchison et al, *N Engl J Med*, 2009).

A profile of telaprevir resistance in a 14-day monotherapy study is shown in Figure 2. Use of a clonal assay that detects variants to a level of 5% of the viral population showed that all patients had wild-type virus at baseline. Some patients had undetectable virus during the 14-day dosing period, but all other patients (exhibiting either

breakthrough or plateau viremia) had resistant mutants detected, with wild-type virus constituting a minority of the population (Sarrazin et al, *Gastroenterology*, 2007). During follow-up of 3 months to 7 months, resistant mutants emerged in patients who had undetectable virus during the 14-day study, and resistant mutants persisted in other patients. The R155K/T and V36M/A mutations were the most persistent, supporting the relative fitness of these mutant variants.

Studies with boceprevir have shown that resistant mutants can still be detected 3 years after drug exposure. The hope had been that because HCV is a “pure” RNA virus with no latent or integrated form, resistance would disappear relatively rapidly. However, these data raise the possibility of rapid reemergence of resistance upon reexposure to drug because of the persistence of relatively fit resistant variants, as occurs with HIV.

Nucleoside Analogue NS5B Polymerase Inhibitor Resistance

Resistance to nucleoside analogue NS5B polymerase inhibitors appears to be more difficult to achieve than with the NS3 protease inhibitors. Identified resistance mutations confer only a modest increase in EC_{50} (eg, 2-fold–5-fold change). Consistent with the concept that the mutations occur in the polymerase’s highly conserved active site, the resistant variants have markedly reduced replication fitness. For example, the S96T resistance mutation causes an approximately 3- to 5-fold increase in EC_{50} versus wild-type virus and has replication fitness of only 5% to 10% of that of wild-type virus. Resistance has not been detected in 14-day monotherapy studies of nucleoside analogue NS5B polymerase inhibitors and generally takes several months to select in vitro. Another consequence of the conservation of the active site is that nucleoside analogue NS5B polymerase inhibitors have exhibited consistent activity across HCV genotypes.

Two distinct resistance patterns have been found with these drugs,

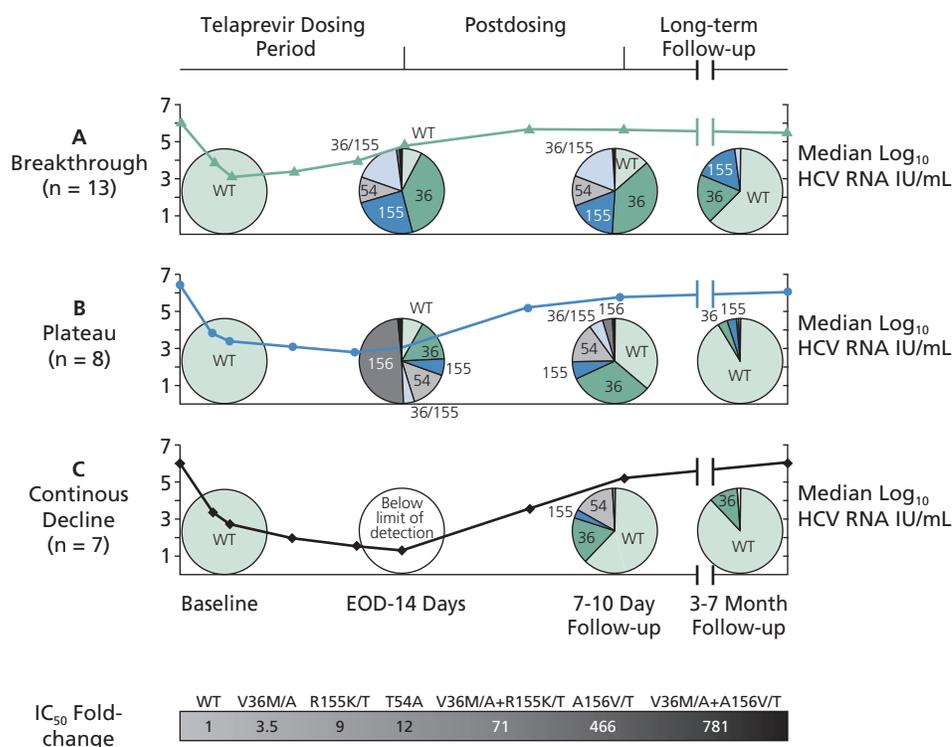


Figure 2. Telaprevir resistance profiles shown as pie charts during and after 14 days of monotherapy. The profiles are shown according to whether patient viral load measures indicated viral breakthrough (panel A), viral load plateau (panel B), or continuous decline (panel C) during the dosing period. Fold-change in the median inhibitory concentration (IC₅₀) associated with various resistance mutations is shown across the bottom. WT indicates wild-type virus; EOD, end of dosing. Adapted from Sarrazin et al, *Gastroenterology*, 2007.

and selection for one makes it difficult to select for the other (Ali et al, *Antimicrob Agents Chemother*, 2008). This scenario raises the possibility that combinations of nucleoside analogues may be able to suppress emergence of viral resistance (Klumpp et al, *J Biol Chem*, 2008; McCown et al, *Antimicrob Agents Chemother*, 2008; Le Pogam et al, *AASLD*, 2007).

Nonnucleoside Analogue NS5B Polymerase Inhibitor Resistance

Resistance to nonnucleoside analogue NS5B polymerase inhibitors emerges rapidly, and resistant mutants often are present before drug exposure. In a study of 92 patients with HCV genotype 1, no patients had nucleoside analogue NS5B resistance at baseline, whereas 21% of patients had preexisting nonnucleoside analogue NS5B inhibitor resistance mutations (simply

reflecting the result of error-prone replication) (Le Pogam et al, *J Antimicrob Chemother*, 2008). Although the percentages of the baseline quasispecies with resistance mutations were only on the order of 1% to 3%, this level is similar to or higher than the baseline percentage that portends virologic failure with nonnucleoside analogue reverse transcriptase HIV inhibitors such as efavirenz.

Interferon Alfa-Free Therapy?

The INFORM-1 (Interferon-Free Regimen for the Management of HCV) trial examined results with 14-day regimens combining the nucleoside analogue NS5B polymerase inhibitor R7128 and the NS3/4A protease inhibitor R7227 (also known as ITMN-191 or danoprevir) in small groups of treatment-naïve and -experienced patients. At the highest dose tested in naïve pa-

tients, 63% (5/8) had undetectable virus (<15 IU/mL) at day 14, a 5.1 log₁₀ IU/mL median decrease in viral load was observed, and no breakthrough resistance was detected (Gane et al, *Lancet*, 2010). Such findings raise the possibility of interferon alfa-free treatment for HCV infection. However, given what is known thus far about resistance to direct-acting antiviral drugs, such treatment will almost certainly require combinations of more than 2 drugs to raise an effective barrier to emergence of resistance.

One current model posits that all single- and 10% to 100% of double-mutant variants, depending on baseline replication levels, are likely to preexist in every HCV-infected patient (with triple mutants expected to be extremely rare). Compensatory mutations will occur within days of drug exposure through drug selective pressure. Thus, for a regimen consisting of only direct-acting agents, a barrier of 4 or more mutations is likely to be needed to prevent loss of virologic control through resistance (Rong et al, *Sci Transl Med*, 2010). It also remains unclear whether treatment can be as successful without the posited benefits of interferon alfa in improving HCV-specific CD4+CD8+ immune cell responses and reversing HCV-associated immunosuppression.

Conclusion

Among the direct-acting antiviral drugs furthest along in development, the NS3 protease inhibitors show potent inhibition (with reductions in viral load of 3 log₁₀ – 4 log₁₀ IU/mL) but a low resistance barrier. Their target geometry is also associated with an increased likelihood of cross-resistance. These drugs are likely to be the first direct-acting drugs approved by the US Food and Drug Administration, with telaprevir and boceprevir both currently in phase III trials.

Among the NS5B polymerase inhibitors, the nucleoside analogues show cross-genotype and cross-subtype activity and exhibit a high resistance barrier (with 2 distinct resistance profiles), but concerns with tolerability and adverse effects remain. The nonnucleo-

side analogue NS5B inhibitors have several target sites, but intrinsic (ie, preexisting) resistance and a low barrier to resistance (including cross-resistance at palm sites) remain problems for this class in general. These drugs have also exhibited variable activity across HCV genotypes and subtypes. The initial use of direct-acting drugs will be as add-on treatment to peginterferon alfa plus ribavirin therapy. The successful development of interferon alfa-sparing regimens depends on achieving a sufficiently high barrier to resistance and whether the immunomodulatory effects of interferon alfa are needed for cure of HCV infection.

Studies are ongoing in patients coinfecting with HIV and HCV, including phase II studies of telaprevir and boceprevir and a pilot trial of nizatamide plus peginterferon alfa and ribavirin. To date, all studies are enrolling interferon alfa-naïve patients with HCV genotype 1 infection. An issue that researchers, academics, and practitioners in infectious diseases should follow is that pharmaceutical companies will develop their own combinations of direct-acting drugs. These combinations may not necessarily reflect the most promising options available from all compounds in development, in terms of activity, tolerability, and resistance emergence. As was done during development of HIV therapeutics, pressure should be brought to advocate for the early study of promising drug combinations, even across company lines, to ensure that patients have access to the best possible treatment regimens as soon as possible.

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Suggested Reading

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