Emerging Therapies for Chronic Hepatitis C Virus

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Abstract: Current hepatitis C virus (HCV) therapies are associated with significant adverse events and less-than-ideal sustained virologic response (SVR) rates in genotype 1 patients. The current standard of care, a combination of pegylated interferon and ribavirin, will likely remain a key component of the treatment regimen for years to come. Multiple new drugs are currently in development and are expected to be approved for use in the United States and/or European Union by 2011 at the earliest. Future therapies will include novel interferons, ribavirin analogues, NS3 HCV protease inhibitors, NS5b HCV polymerase inhibitors, cyclophilin inhibitors, and other novel agents. There is hope that multiple new drugs will be approved over the following 4–10 years to provide alternative treatment choices, improved SVR rates, and reductions in adverse events. However, a number of barriers must be overcome prior to the acceptance of these drugs, involving, but not limited to, their toxicity, viral resistance, optimal dose, duration, and their efficacy and safety in patients with unmet needs.

Keywords
Cyclophilin inhibitor, HCV antiviral therapy, NS3 protease inhibitor, NS5b polymerase inhibitor, pegylated interferon, ribavirin

The hepatitis C virus (HCV) therapies currently in use are associated with significant adverse events and inadequate sustained virologic response (SVR) rates in genotype 1 patients. Pegylated interferon in combination with ribavirin, the current standard-of-care HCV treatment, will likely remain an essential component of the treatment regimen in the future.[1-9] Multiple new drugs are currently being developed and are expected to be approved in the United States and/or European Union by 2011 at the earliest. It is hoped that over the ensuing 4–10 years multiple new drugs will be approved to provide alternative treatment choices as well as improved SVR rates and diminished adverse events associated with HCV treatment. However, a number of challenges must be overcome prior to the approval of these new drugs, involving, but not limited to, toxicity, viral resistance, optimal dose, duration, as well as efficacy and safety in patients with unmet needs. Future therapies will be developed by adding new drugs to the current treatment regimen and determining superiority over the

Table 1. HCV Drugs Currently Under Advanced Study

Drug	Manufacturer	Mechanism of Action
Albumin interferon	Human Genome Sciences/ Novartis	Immunotherapeutic: IFN with a 2–4 week plasma half-life
Taribavirin	Valeant	Immunotherapeutic: RBV analogue (prodrug) to decrease RBV-induced anemia
BILN 2061	Boehringer Ingelheim	Protease inhibitor to HCV NS3
Boceprevir/SCH 503034	Schering-Plough	Protease inhibitor to HCV NS3
Telaprevir/VX-950	Vertex	Protease inhibitor to HCV NS3
R7128	Pharmasset/Roche	NS5b HCV polymerase inhibitor: nucleoside analogue
Valopicitabine/NM-283	Idenix/Novartis	NS5b HCV polymerase inhibitor: nucleoside analogue
R1626	Hoffman-La Roche	NS5b HCV polymerase inhibitor: nucleoside analogue
HCV-796	Viropharma/Wyeth	NS5b HCV polymerase inhibitor: nonnucleoside allosteric inhibitor
DEBIO-025	Debiopharm	Cyclophilin analogue interferes with HCV polymerase
Nitazoxanide	Romark	Unknown mechanism of action

HCV=hepatitis C virus; IFN=interferon; RBV=ribavirin.

current efficacy rates, followed in importance by reducing therapy duration, improving tolerability, and lastly increasing convenience.

A conventional method of evaluating drug therapy is examining the life cycle of the virus and identifying appropriate targets for therapy. The hepatitis C viral life cycle offers a number of potential targets for the interruption of transcription, translation, and viral release. A partial list of compounds in recent development is shown by drug class in Table 1.

Novel Interferons

Albumin interferon (Albuferon, Human Genome Sciences/Novartis) is an 85.7-kd protein formed by the genetic fusion of the human serum albumin gene and the interferon-α gene.[10] This compound was designed to provide a longer therapeutic half-life than that of standard or pegylated interferon. Previous trials have demonstrated that the drug, administered at 900 μg or 1,200 μg via infusion, has significant serum concentrations for 14 days. Phase II data presented in 2007 showed that albumin interferon α-2b administered at 900 μg or 1,200 μg doses every 2 weeks is equivalent in efficacy to pegylated interferon α-2b in combination with weight-based ribavirin in genotype 1 treatment-naive patients.[10] This study demonstrated that SVR-12 (SVR sustained 12 weeks after the end of therapy) rates were essentially equivalent at 54–59% among all groups. Unfortunately, the 1,200-μg dose of albumin interferon was suspected to be associated with pulmonary complications and in some cases interstitial pulmonary fibrosis.[11] Therefore, this treatment arm has been eliminated from phase III trials, and at this time, only 900 μg administered every 2 weeks is being studied to confirm noninferiority against pegylated interferon α-2b or peginterferon α-2a. In two ongoing large phase III trials, it is hoped that this compound will demonstrate efficacy equivalent to that of pegylated interferon along with increased tolerability and improved quality of life. There are currently no studies planned for longer-duration dosing of albumin interferon in HCV patients.

Ribavirin Analogues

Taribavirin (previously known as Viramidine, Valeant Pharmaceuticals) is a ribavirin analogue that has demonstrated a decreased rate of ribavirin-induced anemia. A prodrug of ribavirin, this compound is preferentially absorbed by the liver and converted into ribavirin by the enzyme adenosine deaminase, a process that results in less accumulation and decreased phosphorylation of ribavirin

in red cells, which is the major cause of hemolysis. Unfortunately, 2 large phase III trials of taribavirin that were completed in 2006 failed to demonstrate equivalent efficacy to ribavirin.[12] An ad-hoc subgroup analysis of 1 of these trials indicated that higher SVR rates were seen in patients receiving more than 15 mg/kg of taribavirin and that the rate of anemia in this group was approximately half of the rate of patients treated with ribavirin.[13] A weight-based dosing study of taribavirin versus weight-based ribavirin is currently ongoing.

Protease Inhibitors

The association between SVR and the rapidity of viral clearance has been shown in both retrospective analysis and prospective ongoing study in patients with treatment-naive genotype 1 who were treated with peginterferon α-2a and ribavirin.[14,15] These data clearly demonstrate that patients who achieve rapid virologic response (RVR), defined as undetectable HCV RNA levels via polymerase chain reaction by Week 4, have an excellent chance of attaining SVR if therapy is completed.[14] In addition, patients who become HCV RNA–negative by Week 12, achieving complete early viral response (cEVR), have a 60–72% chance of achieving SVR if therapy is completed, whereas patients who become HCV RNA–negative by Week 24 have a less than 50% chance of achieving SVR.[14]

For this reason, early virologic clearance as defined by RVR and cEVR has been factored into therapy guidance with novel protease and polymerase inhibiting agents.[15,16] HCV utilizes 3 key enzymes for viral replication: NS3 protease, NS3 helicase, and NS5b protease enzymes. Each enzyme has conserved active sites that act as potential drug targets. The NS3 nonstructural protein protease enzyme is a serine-based protease that requires NS4a as a cofactor and has a shallow hydrophobic binding region, making it somewhat difficult to be used for drug development until recent years. The first NS3 protease inhibitor was reported to be effective in humans, but its development has been limited by toxicity.[17]

Since then, 2 important NS3 protease inhibitors have emerged and entered phase III trials, boceprevir (SCH 503034, Schering-Plough) and telaprevir (VX-950, Vertex). At the 2008 European Association for the Study of the Liver (EASL) meeting, data from a phase II study of boceprevir plus pegylated interferon α-2b and ribavirin in treatment-naive subjects with genotype 1 chronic hepatitis C were released for an interim analysis.[18] In this study, 595 patients treated in the United States, Canada, and Europe were randomized to 6 therapy arms in order to determine the efficacy and ideal therapy duration of boceprevir. In 5 treatment arms, patients were treated with pegylated interferon α-2b, ribavirin, and boceprevir 800 mg 3 times daily for a total of 24–48 weeks. In 2 of these treatment arms, a lead-in strategy of 1 month of pegylated interferon α-2b plus ribavirin was used prior to the triple therapy regimen, in contrast to the simultaneous therapy provided in the other 3 arms. The sixth arm consisted of a control group treated with pegylated interferon α-2b and ribavirin in weight-based doses and no boceprevir.

The rate of undetectable HCV RNA by Week 4 was superior in the lead-in arms at 60% versus 39% in patients treated with all 3 drugs simultaneously and 8% in the control group (Roche Taqman, lower level of detection [LLD]=15 IU/mL). SVR-12 rates for the arms of shorter duration were 57% for triple therapy with a lead-in arm versus 55% for simultaneous triple therapy, and RVR showed a high predictability of SVR in both arms. Discontinuation rates in both boceprevir arms were greater than that of the control arm, though adverse events were similar. Viral breakthrough occurred in 4–7% of patients treated with boceprevir, and the compound appeared to be well tolerated, without incidence of rash or pruritus compared to control groups.

This drug has also been studied in combination with pegylated interferon α-2b with and without ribavirin in known null responders who previously failed treatment with pegylated interferon and ribavirin. Unfortunately, the study design for this trial used inadequate doses of boceprevir, ranging from 100 mg to 400 mg TID, or an adequate dose of boceprevir (800 mg TID) with pegylated interferon α-2b but without the addition of ribavirin. The study results yielded poor SVR rates of 2–14% overall[19]; however, it is not clear what the efficacy of this compound would be in partial or slow responders treated with boceprevir 800 mg TID with pegylated interferon and ribavirin.[18,19] Inadequate dosing of boceprevir or the use of the compound without ribavirin results in the emergence of resistant variance in genotype 1 nonresponders who experience inadequate virologic response. Most of these mutations occurred at 5 amino acid positions, with the V170 mutation most prevalent.[20]

The results of the PROVE 1 and 2 trials that evaluated the efficacy of telaprevir in genotype 1 treatment-naive patients were recently presented at the 2008 EASL meeting.[21,22] These results are relevant to treating physicians, as they suggest that 24 weeks of treatment, consisting of 12 weeks with triple therapy (telaprevir/peginterferon α-2a/ribavirin) followed by 12 weeks of consolidation therapy (peginterferon α-2a and ribavirin alone), is as effective as 48 weeks of standard therapy in treatment-naive genotype 1 patients. The results of both PROVE 1 and 2 trials indicated that 79–80% of patients develop undetectable HCV RNA levels using a sensitive assay with a LLD of

10 IU/mL by Week 4 of triple therapy. An RVR-guided regimen is currently being studied with this agent in a phase III trial of treatment-naive patients with genotype 1. It is predicted that 80% of patients in this trial will obtain RVR and therefore receive a shorter duration of therapy; 48 weeks of therapy will be provided to patients who do not attain RVR.

In the PROVE 1 trial, SVR was achieved in 61–65% of patients in the combination telaprevir arms versus 41% in the control arm (P=.02). The relapse rates in both the 24- and 48-week telaprevir arms were very low (2% and 6%, respectively), and adverse events associated with telaprevir were primarily limited to skin rash, which was rated as severe in 7% of patients. The PROVE 2 trial demonstrated that all the rashes occurred after 8 weeks of therapy; therefore, a shorter treatment regimen of triple therapy for 8 weeks is planned for a future phase III trial. A limited number of patients also developed gastrointestinal events and mild anemia. The RVR and SVR rates in the PROVE 2 trial were similar to those in the PROVE 1 trial. The PROVE 2 study also included one arm with treatment limited to 12 weeks and a treatment arm without ribavirin. Both of these arms were inferior to triple therapy for 12 weeks followed by 12 weeks of consolidation therapy with peginterferon and ribavirin.

A third important study of telaprevir in prior pegylated interferon plus ribavirin nonresponders or relapsers was also presented at the 2008 EASL meeting.[23] This was the first study to show improved RVR rates in previous treatment failures. Although the number of patients was relatively small, previous nonresponders experienced an RVR rate of 75%, partial responders achieved an RVR rate of 95%, and relapsers achieved an RVR rate of 100%. Subsequent SVR-12 data have been released demonstrating SVR rates in relapsers of 73% and more than 40% in nonresponders.[24] These data are the first to show improved responses in previous nonresponders and have led to a phase III trial in treatment-failure patients scheduled to begin in 2008.

Studies using serum samples from patients treated in the telaprevir trials have revealed mutations that confer high-level resistance with monotherapy.[25] Thus far, all telaprevir-resistant mutants are sensitive to interferon α, so combination therapy prevents development of resistant isolates.[26] The T54A mutation confers resistance to both telaprevir and boceprevir.[27]

Polymerase Inhibitors

Viral polymerase enzymes are essential for replication, and polymerase inhibitors form the largest class of antiviral drugs with proven efficacy in hepatitis B virus, herpes simplex virus, and HIV infection. It is therefore reasonable to think that polymerase inhibitors will become an important therapy for hepatitis C. A large proportion of polymerase inhibitors are nucleoside analogues, which, following enzymatic conversion to the corresponding nucleoside triphosphate, competitively inhibit viral nucleic acid synthesis.[28] A number of such compounds are currently in development, but those currently farthest along are R1626 and R7128 (Hoffman-LaRoche and Pharmasset/Roche, respectively).[29,30] R1626 is a tri-isobutyl ester prodrug of the nucleoside analogue R1479. This compound is phosphorylated in the hepatocyte to the active moiety R1479-TP, which is a potent and selective inhibitor of the NS5b viral RNA-dependent RNA polymerase enzyme. This compound therefore acts as a chain terminator, inhibiting RNA extension into nascent HCV RNA. The R7128 drug is a potent nucleoside inhibitor of HCV polymerase, which is not converted in the gut but which acts as a chain terminator to inhibit RNA extension in a similar fashion to R1479-TP.[31]

The results of a phase IIa trial using R1626 in combination with pegylated interferon α-2a and ribavirin were presented by Nelson and associates at the 2008 EASL meeting.[29] The data showed that, when combined with peginterferon α-2a and ribavirin, this compound had high RVR rates (81%) and high 48-week end-of-treatment responses (84%; HCV RNA levels assessed by Taqman assay, LLD=15 IU/mL). This was an improvement over a control arm of standard pegylated interferon and ribavirin with an end-of-treatment response rate of 65%. Data showing final SVR rates are pending at this time, making it unclear whether the improved end-of-treatment response rates seen with triple therapy will be maintained without significant relapse. Although the compound has been proven to be quite potent, there are significant toxicity concerns that the dose-dependent rate for neutropenia seen in all arms of the study would require dose reduction or cessation of therapy prematurely in many patients.

A subsequent phase IIb trial has been designed and is currently underway to determine whether a safe and effective combination regimen can be utilized to retain the benefit of the compound without the safety concerns. R1626 has shown a low level of resistance and the absence of resistant mutations in both monotherapy and combination therapies, suggesting that this polymerase inhibitor will have a high barrier to resistance.[32]

Results of an interim analysis of R7128 administered at doses of 500 mg or 1,500 mg BID in combination with pegylated interferon α-2a and ribavirin were also presented at the 2008 EASL meeting.[30] These results clearly demonstrated excellent efficacy of 1,500 mg BID dosing, with RVR rates of 85% (Taqman assay, LLD=15 IU/mL) as compared to 30% for the 500 mg dose and 10% for the control arm. No toxicities were associated with 4 weeks of

therapy; specifically, no evidence of neutropenia or rash was seen. These data led to phase IIb trials evaluating 12 weeks of triple therapy followed by 12 weeks of consolidation therapy with a study design similar to that of the telaprevir trials. Investigation of 1,500 mg BID dosing in genotype 2-3 patients who were prior treatment failures has reported 90% of patients to be HCV RNA undetectable at Week 4.[33]

Other Novel Compounds

The HCV polymerase enzyme offers other avenues of targets, one of which has been developed in the form of a cyclosporine inhibitor. One such compound, Debio-025, is a small oral molecule that is an inhibitor of cyclophilin. Administered over a 14-day period in combination therapy in HIV/HCV co-infected patients, this compound has yielded a greater than 3-log reduction in viral load.[34] This drug is currently being studied in combination with pegylated interferon and ribavirin in genotype 1 patients with previous treatment failure.

A second compound, nitazoxanide (Alinia, Romark), was recently studied in genotype 4 patients who were previously untreated and is licensed in the United States for the treatment of diarrhea caused by *Cryptosporidium partum* and *Giardia lamblia*. This drug has activity against a number of viruses and therefore has been studied in both chronic hepatitis B and C. Its mechanism of action against viruses is unknown but differs against anaerobic bacteria and protozoa. A recent randomized controlled study in patients with treatment-naive genotype 4 showed improved efficacy in patients who received triple therapy with nitazoxanide, pegylated interferon α-2a, and ribavirin versus those who received nitazoxanide and pegylated interferon α-2a or those who received standard-of-care treatment (SVR rates of 79%, 61%, and 50%, respectively).[35] The adverse events were the same in all 3 arms, suggesting that there was no added side effects from the study compound. The authors concluded that this drug should be studied in a larger trial evaluating genotype 1 patients, which is currently being planned. The results of the initial trial appeared to be almost too favorable to be credible, and the drug is well tolerated and currently available in the United States. However, the study was limited by its small number of treatment arms and by the fact that a significant difference was seen in the SVR rate of the control arm (59%) and the rate previously presented in other data (79%).[15]

Summary

In conclusion, it is anticipated that new drugs will be available that will enhance treatment of hepatitis C infection, particularly in genotype 1 patients. A large number of these drugs are currently in development, though it is expected that many of them will not ultimately be approved by the United States Food and Drug Administration. However, a number of compounds appear promising at this time and have entered phase III trials, indicating a markedly improved chance of success. The earliest that the first of these drugs, telaprevir and/or boceprevir, are expected to be approved would be 2011; it is hoped that this will then be followed by the emergence of numerous new compounds over the ensuing 5–10 years. The ultimate goals are to improve efficacy for all patients, enhance tolerability, and shorten the duration of treatment.

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References

1. US Food and Drug Administration. Antiviral Drugs Committee Briefing Document. Pegylated interferon-α_{2a} (Pegasys®). November 14, 2002. Available at: http://www.fda.gov/ohrms/dockets/ac/02/briefing/3909b1.htm.
2. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C. *Hepatology*. 2002;36(5 suppl 1):S3-S20.
3. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001;358: 958-965.
4. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, et al. Peginterferon-α_{2a} in patients with chronic hepatitis C. *N Engl J Med*. 2000;343:1666-1672.
5. Heathcote EJ, Shiffman ML, Cooksley WG, Dusheiko GM, Lee SS, et al. Peginterferon-α_{2a} in patients with chronic hepatitis C and cirrhosis. *N Engl J Med*. 2000;343:1673-1680.
6. Reddy KR, Wright TL, Pockros PJ, Shiffman M, Everson G, et al. Efficacy and safety of pegylated (40-kd) interferon-α_{2a} compared with interferon-α_{2a} in noncirrhotic patients with chronic hepatitis C. *Hepatology*. 2001;33:433-438.
7. Pockros PJ, Carithers R, Desmond P, Dhumeaux D, Fried MW, et al. Efficacy and safety of two-dose regimens of peginterferon-α_{2a} compared with interferon-α_{2a} in chronic hepatitis C: a multicenter, randomized controlled trial. *Am J Gastroenterol*. 2004;99:1298-1305.
8. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347:975-982.
9. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, et al. Peginterferon-α_{2a} and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004;140:346-355.
10. Nelson D, Rustgi V, Balan V, Lambiase L, Davis G, et al. A phase 2 study of Albuferon in combination with ribavirin in non-responders to prior interferon therapy for chronic hepatitis C. *Hepatology*. 2005;42(suppl 1):278A.
11. Human Genome Sciences modifies dosing in Achieve trials of albuferon [press release]. Cambridge, MA: Human Genome Sciences; January 23, 2008.
12. Benhamou Y, Pockros P, Rodriguez-Torres M, Gordon S, Shiffman M, et al. The safety and efficacy of viramidine plus pegylated interferon alfa-2B versus ribavirin plus pegylated interferon alfa-2B in therapy-naïve patients infected with HCV: phase 3 results. *J Hepatol*. 2006;44:837-1012.
13. Pockros PJ, et al. Taribavirin exposure analysis from a previous phase 3 trial correlates with phase 2b weight-based dosing interim results. *Hepatology*. In press.
14. Ferenci P, Fried MW, Shiffman ML, Smith CI, Marinos G, et al. Predicting sustained virologic response in chronic hepatitis C patients treated with peginterferon alfa 2a (40 kD)/ribavirin. *J Hepatol*. 2005;43:425-433.

15. Fried MW, Hadziyannis SJ, Shiffman M, Messinger D, Zeuzem S. Rapid virologic response is a more important predictor of sustained virologic response (SVR) than genotype in patients with hepatitis C virus infection. *J Hepatol.* 2008;48(suppl 2):S5.
16. Shiffman ML, Chung RT, Hamzeh FM. Time to HCV RNA undetectability supersedes baseline factors in predicting SVR in patients with HCV genotype 1. *J Hepatol.* 2008;48(suppl 2):S313.
17. Lamarre D, Anderson PC, Bailey M, Beaulieu P, Bolger G, et al. An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. *Nature.* 2003;426:186-189.
18. Kwo P, Lawitz E, McCone J, Schiff E, Vierling J, et al. Interim results from HCV SPRINT-1: RVR/EVR from phase 2 study of boceprevir plus peginterferon alfa-2b/ribavirin in treatment-naïve subjects with genotype-1 CHC. *J Hepatol.* 2008;48(suppl 2):S372.
19. Schiff E, Poordad F, Jacobson I, Flamm S, Bacon B, et al. Boceprevir combination therapy in null responders: response dependent on interferon responsiveness. *J Hepatol.* 2008;48(suppl 2):S46.
20. Susser S, Welker MW, Zettler M, Wohnsland A, Hughes E, et al. Clonal analysis of mutations selected in the HCV NS3 protease domain of genotype 1 non-responders treated with bocepravir (SCH503034). *J Hepatol.* 2008; 48(suppl 2):S29.
21. McHutchison JG, Everson GT, Gordon SC, Jacobson I, Kauffman R, et al. PROVE 1: results from a phase 2 study of telaprevir with Peginterfeon alfa-2a and ribavirin in treatment-naïve subjects with hepatitis C. *J Hepatol*. 2008; 48(suppl 2):S4.
22. Dusheiko GM, Hezode C, Pol S, Goeser T, Bronowicki J-P, et al. Treatment of chronic hepatitis C with telaptrevir (TVR) in conbination with peginterferon alfa-2a with or without ribavirin: further interim analysis results of the PROVE 2 Study. *J Hepatol.* 2008;48(suppl 2):S26.
23. Poordad F, Shiffman ML, Sherman K, Smith J, Yao M, et al. A study of telpravir with peginterferon alfa-2a and ribavirin in subjects with well-documented prior PR null response, non-response or relapse: preliminary results. *J Hepatol.* 2008;48(suppl 2):S374.
24. Vertex reports 52% SVR12 rate for a 24-week telaprevir-based regimen in genotype 1 hepatitis C patients who failed prior treatment [press release]. Cambridge, MA: Vertex Pharmaceuticals; June 9, 2008.
25. Sarrazin C, Kieffer TL, Bartels D, Hanzelka B, Muh U, et al. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telapravir. *Gastroeneterology.* 2007;132:1767-1777.
26. Manns MP, Foster GR, Rockstroh JK, Zeuzem S, Zoulin F, Houghton M. The way forward in HCV treatment--finding the right path. *Nat Rev Drug Discov.* 2007;6:991-1000.
27. Tong X, Chase R, Skelton A, Chen T, Wright-Minogue J, Malcolm BA. Identification and analysis of resistance mutations against the HCV protease SCH 502024. *Antiviral Res.* 2006;70:28-38.
28. Pawlotsky JM. Treating hepatitis C in "difficult-to-treat" patients. *N Engl J Med.* 2004;351:422-423.
29. Nelson D, Pockros PJ, Godofsky E, Rodriguez-Torres M, Everson G, et al. High end-of-treatment response (84%) after 4 weeks of R1626, peginterferon alfa-2a and ribavirin followed by a further 44 weeks of peginterferon alfa-2a and ribavirin. *J Hepatol.* 2008;48(suppl 2):S371.
30. Lalezari J, Gane E, Rodriguez-Torres M, De Jesus E, Nelson D, et al. Potent antiviral activity of the HCV nucleoside polymerase inhibitor R7128 with PEG-IFN and ribavirin: interim results of R7128 500 mg BID for 28 days. *J Hepatol.* 2008;48(suppl 2):S29.
31. Klumpp K, Leveque V, Le Pogam S, Ma H, Jiang WR, et al. The novel nucleoside analog R1479 (4'-azidocytidine) is a potent inhibitor of NS5B-dependent RNA synthesis and hepatitis C virus replication in cell culture. *J Biol Chem.* 2006;281:3793-3799.
32. LePogam S, Seshaadri A, Kang H, Kosaka A, Hu S, et al. Low level of resistance, low viral fitness and absence of resistance mutations in baseline quasispecies may contribute to high barrier to R1626 resistance in vivo. *J Hepatol.* 2008;48(suppl 2):S10.
33. Pharmasset reports preliminary results of a 4-week proof-of-concept combination study of R7128 for the treatment of chronic hepatitis C in genotype 2 or 3 non-responders [press release]. Princeton, NJ: Pharmasset, Inc; September 8, 2008.
34. Flisiak R, Horban A, Gallay P, Bobardt M, Selvarajah S, et al. The cyclophilin inhibitor Debio-025 shows potent anti-hepatitis C effect in patients coinfected with hepatitis C and human immunodeficiency virus. *Hepatology*. 2008;47: 817-826.
35. Rossignol J-F, Elfert A, Keefe EB. Evaluation of a 4 week lead-in phase with nitazoxanide prior to nitazoxanide + peginterferon in treating chronic hepatitis C. *J Hepatol.* 2008;48(suppl 2):S312.