Dear Colleague:

For most patients infected with hepatitis C virus (HCV), the current pharmacologic standard of care is peginterferon in combination with ribavirin. With this therapeutic approach, HCV is a highly treatable disease for patients with acute hepatitis C or chronic hepatitis C genotype 2 or 3 infection. However, approximately 50% of patients infected with HCV genotype 1 do not achieve a sustained virologic response (SVR) with initial interferon-based therapy, and retreatment has yielded poor results. For patients who have failed interferon-based therapy or for those with contraindications to interferon, current curative treatment options are limited. As the population of nonresponders grows larger, the need for novel approaches to HCV care grows more urgent.

As our understanding of HCV infection evolves, many novel HCV therapies are being developed. Encouraging data are emerging from a range of treatment strategies, from entirely novel anti-HCV drug classes to modifications of current therapies. Initial clinical findings of many of these new agents were presented at The Liver Meeting 2004, which was held October 28 through November 2 in Boston, Mass. Although these agents are in the early stages of clinical development, they preview an exciting future of new therapeutic options for patients with intractable HCV infection.

In this newsletter, we highlight the latest findings on selected novel HCV therapies reported at The Liver Meeting 2004. In addition, we invite you to listen to expert commentary on these promising future HCV therapies, exclusively at www.projectsinknowledge.com/HCVPipeline. This discussion is not meant to be all-inclusive, but rather encompasses some of the more promising approaches currently being evaluated for the treatment of HCV.

Sincerely,

Chair

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Want to listen to what the experts have to say about the promising future HCV therapies discussed in this Tx Reporter?

Visit www.projectsinknowledge.com/HCVPipeline, and look for the microphone icons within the online (HTML) version to access the audio commentary.
Introduction

Given the current state of drug development, it is unlikely that any new therapies for hepatitis C virus (HCV) infection—regardless of how compelling the early clinical data—will be licensed in the immediate future. Despite this limitation, patients and physicians continue to share an intense interest in novel anti-HCV therapies, and research in this area is evolving at a rapid pace. The studies summarized here represent different mechanisms of action and stages of clinical development, and together provide a snapshot of the exciting data presented at The Liver Meeting 2004.

Novel agents for the treatment of HCV can be described as predominantly immunomodulatory or antiviral in nature. Immune modulators trigger or supplant the endogenous anti-HCV immune response, whereas antiviral drugs inhibit HCV replication. As with standard interferon therapy, some new treatments—particularly the alternative interferons—may combine both immunomodulatory and antiviral effects.

Nucleoside Analog

Viramidine

Background

Ribavirin, combined with pegylated interferon-alfa, is effective in achieving sustained viral response (SVR) in the majority of hepatitis C patients, but it can be associated with hemolytic anemia. In a review of two trials enrolling 677 HCV patients, Sulkowski and colleagues found that more than 50% of patients treated with pegylated interferon-alfa and ribavirin report decreases in hemoglobin (Hgb) of ≥3.0 g/dL. Viramidine, a ribavirin produg, escapes this dose-limiting toxicity by being preferentially taken up by the liver, resulting in lower ribavirin levels in the peripheral circulation.

AASLD Update

Two studies reported in poster sessions clarified the potential role of oral viramidine in treatment-naive HCV-infected patients. Lin et al found that viramidine yielded lower mean ribavirin concentrations in plasma and red blood cells (RBCs) and a smaller mean decrease in Hgb levels compared with ribavirin. In an open-label, randomized trial, 87 treatment-naive HCV-infected patients received either viramidine, a ribavirin 600 mg BID or 600 mg AM and 400 mg PM (n = 42) or weight-based ribavirin 600 mg twice daily (n = 42) or weight-based ribavirin 600 mg BID or 600 mg AM and 400 mg PM (n = 45). Measurements of Hgb and ribavirin levels in plasma and RBCs were taken at baseline and at weeks 12 and 24. Viramidine resulted in lower mean drug concentrations compared with ribavirin in both plasma (0.931 µg/mL versus 1.88 µg/mL) and RBCs (145 µg/mL versus 251 µg/mL). Viramidine also caused a smaller mean decrease in Hgb compared with ribavirin (11.4% versus 19.7%). These effects, observed initially at week 12, remained steady through week 24.

Overall, the findings of this study suggest that the potential to develop hemolytic anemia is much lower with viramidine than with ribavirin. In a phase II dose-ranging study of 180 treatment-naive HCV-infected patients, Gish et al compared the safety and antiviral efficacy of viramidine and ribavirin. Participants receiving subcutaneous pegylated interferon alfa-2a 180 µg/wk were randomized to receive oral ribavirin 400 mg (n = 47), 600 mg (n = 43), or 800 mg (n = 45) twice daily or ribavirin 1000 to 1200 mg/d (n = 45). Patients with genotype 2 or 3 infection were treated for 24 weeks, and those with genotype 1, 4, 5, or 6 infection were treated for 48 weeks.

Patients had a median HCV RNA of 6.5 log₁₀ copies/mL at baseline. At the end of treatment, no significant differences were found between the viramidine and ribavirin treatment groups in the proportion of patients with undetectable HCV RNA levels (range, 55%-63%), regardless of HCV genotype (Figure 1a, see page 3). However, the incidence of anemia was significantly lower among patients treated with 400 mg or 600 mg BID viramidine compared with those treated with 1000 to 1200 mg/d ribavirin (P < .01) (Figure 1b, see page 3). All other adverse events were similar between treatment arms. Final safety and SVR data are expected in 2005.

Given the equivalent efficacy and lower incidence of anemia with viramidine compared with ribavirin, 600 mg BID viramidine was identified as the best dose to evaluate in phase III viramidine trials.

Immune System Modulators

IC41 Vaccine

Background

Vaccination with synthetic HCV peptides induces IFN-gamma–secreting cytotoxic and helper T-cell responses with the T-cell adjuvant poly-L-arginine. The new synthetic peptide IC41 vaccine, which contains cytotoxic and helper T-cell epitopes of HCV, may generate a similar immunologic response.

AASLD Update

Two studies reported in poster sessions clarified the potential role of oral viramidine in treatment-naive HCV-infected patients. Lin et al found that viramidine yielded lower mean ribavirin concentrations in plasma and red blood cells (RBCs) and a smaller mean decrease in Hgb levels compared with ribavirin. In an open-label, randomized trial, 87 treatment-naive HCV-infected patients received either viramidine, a ribavirin 600 mg twice daily (n = 42) or weight-based ribavirin 600 mg BID or 600 mg AM and 400 mg PM (n = 45). Measurements of Hgb and ribavirin levels in plasma and RBCs were taken at baseline and at weeks 12 and 24. Viramidine resulted in lower mean drug concentrations compared with ribavirin in both plasma (0.931 µg/mL versus 1.88 µg/mL) and RBCs (145 µg/mL versus 251 µg/mL). Viramidine also caused a smaller mean decrease in Hgb compared with ribavirin (11.4% versus 19.7%). These effects, observed initially at week 12, remained steady through week 24. Overall, the findings of this study suggest that the potential to develop hemolytic anemia is much lower with viramidine than with ribavirin. In a phase II dose-ranging study of 180 treatment-naive HCV-infected patients, Gish et al compared the safety and antiviral efficacy of viramidine and ribavirin. Participants receiving subcutaneous pegylated interferon alfa-2a 180 µg/wk were randomized to receive oral ribavirin 400 mg (n = 47), 600 mg (n = 43), or 800 mg (n = 45) twice daily or ribavirin 1000 to 1200 mg/d (n = 45). Patients with genotype 2 or 3 infection were treated for 24 weeks, and those with genotype 1, 4, 5, or 6 infection were treated for 48 weeks. Patients had a median HCV RNA of 6.5 log₁₀ copies/mL at baseline. At the end of treatment, no significant differences were found between the viramidine and ribavirin treatment groups in the proportion of patients with undetectable HCV RNA levels (range, 55%-63%), regardless of HCV genotype (Figure 1a, see page 3). However, the incidence of anemia was significantly lower among patients treated with 400 mg or 600 mg BID viramidine compared with those treated with 1000 to 1200 mg/d ribavirin (P < .01) (Figure 1b, see page 3). All other adverse events were similar between treatment arms. Final safety and SVR data are expected in 2005. Given the equivalent efficacy and lower incidence of anemia with viramidine compared with ribavirin, 600 mg BID viramidine was identified as the best dose to evaluate in phase III viramidine trials. Given the equivalent efficacy and lower incidence of anemia with viramidine compared with ribavirin, 600 mg BID viramidine was identified as the best dose to evaluate in phase III viramidine trials. Given the equivalent efficacy and lower incidence of anemia with viramidine compared with ribavirin, 600 mg BID viramidine was identified as the best dose to evaluate in phase III viramidine trials. Given the equivalent efficacy and lower incidence of anemia with viramidine compared with ribavirin, 600 mg BID viramidine was identified as the best dose to evaluate in phase III viramidine trials. Given the equivalent efficacy and lower incidence of anemia with viramidine compared with ribavirin, 600 mg BID viramidine was identified as the best dose to evaluate in phase III viramidine trials. Given the equivalent efficacy and lower incidence of anemia with viramidine compared with ribavirin, 600 mg BID viramidine was identified as the best dose to evaluate in phase III viramidine trials.
Among the 36 patients receiving active IC41 vaccine, 21 had a T-cell response, and 6 of these showed transient reduction in HCV RNA. IC41 immunization induced CD8+ helper T-cells in all three treatment groups and in the poly-L-arginine control group, but not in the peptide-only control group. This suggests that poly-L-arginine must be present to induce IFN-gamma-secreting T-cells. CD8+ cytotoxic T-cells were induced in the three IC41 treatment groups only. Increasing numbers of vaccinations led to higher response rates and more robust responses.

IC41 was well tolerated, with transient local injection-site reactions, including pain, itching, induration, edema, and erythema. These reactions did not worsen with an increasing number of vaccinations. Discontinuations due to adverse events were rare (1.67%).

These findings suggest that IC41 is a safe, well-tolerated fully synthetic therapeutic peptide vaccine. Additionally, in nonresponders to and relapsers following standard therapy, IC41 vaccine is capable of inducing both IFN-gamma-secreting cytotoxic and helper T-cells.

**CPG 10101**

**Background**

CPG 10101 is a member of a new class of synthetic antiviral immune modulators that act as agonists of toll-like receptors, which play a critical role in the recognition and activation of pathogens by the immune system. CPG 10101 selectively induces cytokines and chemokines, including IFN-alpha, IFN-gamma inducible protein-10 (IP-10), and 2’5’-oligoadenylate synthetase (OAS), an interferon-stimulated gene.

**AASLD Update**

In the first clinical trial of this agent, McHutchison and colleagues showed that CPG 10101 induces high levels of endogenous interferon gamma, helping to restore immune function that is compromised by chronic viral infection. In the phase 1b study, 31 patients who either had relapsed after interferon-based therapy or were treatment naive for anti-HCV therapy were randomized to control (n = 7) or CPG 10101 (n = 24) in five sequential dose groups (0.25 mg, 1 mg, 4 mg, 10 mg, 20 mg). Data from an ongoing fifth treatment arm of CPG 10101 20 mg was not included in this analysis. Patients received subcutaneous CPG 10101 twice weekly for 4 weeks and were monitored for an additional 4 weeks.

Innate immune response was activated 24 hours after the first CPG 10101 injection in patients treated with low-dose CPG 10101, including 0.25 mg (n = 4) and 1.0 mg (n = 6). Compared with baseline, serum IP-10 levels increased 1.2- to 8.4-fold. This CPG 10101-induced immunologic response also translated into antiviral activity. Among those who received 1, 4, or 10 mg CPG 10101 (n = 18), six patients had a ≥1-log reduction in HCV RNA and three had a ≥2-log reduction. RNA reductions were seen in patients with HCV genotypes 1a (n = 3), 1b (n = 2), and 2b (n = 1). Viral RNA levels were reduced from days 1 to 29 but rebounded after dosing was completed.

Local injection site reactions, which reflect the immunostimulatory action of CPG 10101, included erythema, pain, pruritus, inflammation, and swelling. At the highest dose (10 mg), there was one report each of grade 3 fatigue, asthenia, pyrexia, rigors, and back pain, and two reports each of arthralgia and myalgia. One patient (4 mg) developed grade 3 neutropenia and one other patient (10 mg) withdrew due to grade 2 vomiting and diarrhea. No clinically significant changes in alanine aminotransferase (ALT), aspartate aminotransaminase (AST), or creatinine phosphokinase were observed. Results of additional dose escalation to 20 mg are pending.

**Isatoribine**

**Background**

Another toll-like receptor agonist, isatoribine is a guanosine analog that activates innate immunity. Although isatoribine has no direct in vitro activity against RNA or DNA viruses, it is thought to accelerate HCV clearance by increasing localized cytokine signaling.

**AASLD Update**

Horsmans and colleagues reported that treatment with isatoribine significantly reduced plasma HCV RNA while avoiding the adverse effects associated with interferon-based therapy.

Of the 25 patients enrolled in the proof-of-concept trial, 15 were treatment-naive and 10 had relapsed from interferon-based therapy. Patients were treated with intravenous isatoribine (60–80-min infusion) 200 to 800 mg once daily for 7 days, during which serial blood samples were collected and assayed for plasma isatoribine, plasma HCV RNA, and expression of 2’5’-OAS, which is typically induced by interferon. Isatoribine was eliminated with a short half-life (~2 h) and plasma clearance (~30 L/h) that was independent of dose. Isatoribine did not accumulate in plasma during once-daily dosing. After 7 days of treatment, OAS expression in blood was increased and plasma HCV RNA was decreased, with changes from baseline that
Table 1. Effects of Isatoribine on Plasma HCV RNA and OAS Levels

<table>
<thead>
<tr>
<th>Isatoribine (mg/d)</th>
<th>Patients (N)</th>
<th>HCV Genotype 1 N (%)</th>
<th>Mean ± SD Baseline Plasma HCV RNA (Log IU/mL)</th>
<th>Mean ± SD Log Viral Load Change, EOT Minus Baseline</th>
<th>Mean ± SD Blood OAS Ratio EOT, Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>4</td>
<td>3 (75%)</td>
<td>6.4 ± 0.1</td>
<td>-0.03 ± 0.16</td>
<td>3.4 ± 2.3</td>
</tr>
<tr>
<td>400</td>
<td>4</td>
<td>1 (25%)</td>
<td>5.7 ± 0.2</td>
<td>-0.39 ± 0.44</td>
<td>4.5 ± 3.1</td>
</tr>
<tr>
<td>600</td>
<td>5</td>
<td>3 (60%)</td>
<td>5.9 ± 0.6</td>
<td>-0.24 ± 0.28</td>
<td>7.5 ± 2.0*</td>
</tr>
<tr>
<td>800</td>
<td>12</td>
<td>10 (83%)</td>
<td>5.5 ± 0.6</td>
<td>-0.76 ± 0.81*</td>
<td>7.5 ± 5.3*</td>
</tr>
</tbody>
</table>

*P < .01, paired t-test versus baseline; EOT = end of treatment; OAS = oligoadenylate synthetase.

were statistically significant at the 800 mg/d dose (Table 1). After a 7-day washout, OAS expression and plasma HCV RNA returned to pretreatment levels.

Isatoribine appears to be safe and well tolerated, with no reports of serious adverse events and no discontinuations due to adverse events or clinical laboratory abnormalities. The most frequent adverse events were insomnia (n = 4), joint pain (n = 4), and asthenia (n = 3), all of which were mild or moderate.

Inhibitors of Viral Replication

Merimepodib

**Background**

Merimepodib selectively inhibits inosine monophosphate dehydrogenase, an enzyme believed to be important to HCV replication. At the annual meeting of the European Association for the Study of the Liver in April 2004, Marcellin et al reported that merimepodib improved the antiviral effect of peginterferon alfa-2b and ribavirin combination therapy in patients who did not respond to standard interferon plus ribavirin.

**AASLD Update**

In a phase Ia study reported by Zha et al, merimepodib enhanced the antiviral effect of peginterferon/ribavirin combination therapy without exacerbating ribavirin-associated anemia. The study enrolled 31 patients with genotype 1 infection who were nonresponsive to interferon/ribavirin therapy. Patients were given peginterferon/ribavirin and one of three study treatments: placebo, merimepodib 25 mg every 12 hours, or merimepodib 50 mg every 12 hours. Pharmacokinetic and pharmacodynamic parameters included steady-state area under the plasma concentration-time curve (AUC_{ss,12h}) and trough plasma concentration (C_{tough}) of ribavirin.

At week 12, patients were categorized as virologic responders (≥2-log drop in HCV RNA viral load) or nonresponders. Virologic responders had a significantly higher merimepodib AUC_{ss,12h} compared with nonresponders (P = .0103). Given that virologic responses were seen in 0%, 60%, 12 hours. Pharmacokinetic and pharmacodynamic parameters included steady-state area under the plasma concentration-time curve (AUC_{ss,12h}) and trough plasma concentration (C_{tough}) of ribavirin.

At week 12, patients were categorized as virologic responders (≥2-log drop in HCV RNA viral load) or nonresponders. Virologic responders had a significantly higher merimepodib AUC_{ss,12h} compared with nonresponders (P = .0103). Given that virologic responses were seen in 0%, 60%, and 80% of patients in quartiles 1, 2, 3, and 4, respectively, of merimepodib exposure, this relationship appears to follow a linear dose-response curve. Younger age and ribavirin C_{tough} levels were the only other significant predictors of virologic response at week 12. In addition, anemia was correlated with ribavirin C_{tough} levels but not with merimepodib exposure. On the basis of these findings, higher doses (50 and 100 mg every 12 hours) of merimepodib are being explored in a phase IIb study.

**NM283**

**Background**

NM283 is an RNA polymerase inhibitor with antiflavivirus activity in vitro and in HCV-infected chimpanzees. Earlier this year, Godofsky et al reported findings from a phase I/II study that showed NM283 has consistent, dose-related antiviral activity against genotype 1 HCV.

**AASLD Update**

Afzal and colleagues reported findings of a phase I/II dose-escalation study of NM283 in difficult-to-treat, predominantly nonresponding patients infected with genotype 1 HCV. Patients in eight sequential cohorts were randomized to increasing doses (50–800 mg/d) of NM283 or placebo for 15 days and monitored for an additional 2 weeks. Among the 94 patients who completed the study, 13% were treatment naive and 87% were prior nonresponders to interferon-based therapies.

NM283 consistently reduced HCV RNA levels in all dose groups, ranging from a mean 0.2 log_{10} reduction at the lowest dose (50 mg/d) to a mean 1.2 log_{10} reduction at the 800 mg/d dose. Among those treated with 800 mg/d, individual patient HCV RNA reductions ranged from 0.41 log_{10} (61% reduction) to 2.37 log_{10} (>99% reduction). By contrast, HCV RNA levels rose by 0.03 log_{10} (7% increase) among patients treated with placebo.

No serious adverse events, treatment-limiting toxicities, patterns of laboratory abnormalities, or adverse-event–related discontinuations were reported in this study. The most common adverse event was nausea with occasional vomiting, which was mild, self-limited, and more frequent with NM283 doses ≥400 mg/d.

In addition to reporting results of the dose-escalation study, Afzal also presented initial findings of an ongoing phase II trial of NM283 in combination with peginterferon. For the 28-day trial, 30 patients were randomized to NM283 monotherapy (n = 12 patients) or NM283 plus 1 µg/kg subcutaneous peginterferon on days 8, 15, and 22 (n = 18). In all patients, NM283 was titrated to 800 mg/day by day 8.

To date, 19 patients have completed 28 days of treatment. Overall, these patients have experienced a mean 0.7-log reduction in HCV RNA. Among the 12 patients who received combination therapy, nine patients achieved ≥1-log_{10} reduction by week 4, suggesting that the combination of NM283 and peginterferon may result in synergistic antiviral activity.

Given the promising early findings of the phase II trial, expanded clinical testing of NM283, alone and in combination with peginterferon, is currently under way.

**Alternative Interferon**

**Albumin-interferon alfa**

**Background**

Albumin-interferon alfa is a new 87.5 kDa recombinant polypeptide consisting of interferon-alfa genetically fused to human serum albumin. The resulting fusion protein combines the antiviral properties of interferon-alfa with the long serum half-life of albumin.

**AASLD Update**

Balan and colleagues presented data that show that nearly half of HCV-infected patients who have failed prior interferon-based therapy can achieve an antiviral response with the albumin-interferon alfa fusion protein.

The phase I/II, open-label, albumin-interferon dose escalation study enrolled 119 patients (93% HCV genotype 1) who failed prior interferon-based therapy. Patients received 7 to 900 µg albumin-interferon in one or two subcutaneous injections every 2 weeks for a mean treatment period of 68 weeks.

Albumin-interferon reduced HCV RNA by at least 0.5 log_{10} in each dose group (Figure 2, see page 5). Among patients receiving 120 to 900 µg albumin-interferon (n = 78), 47% achieved an antiviral response (≥1-log reduction at any time point). In addition, gene expression analysis showed that interferon response genes were induced. Viral kinetics shows a biphasic decline of HCV RNA after administration of albumin-interferon.
Over the 120 to 600 µg dose range, median terminal half-life was approximately 143 hours. Given its reduced clearance and extended half-life, the pharmacokinetic profile of albumin-interferon supports dosing every 2 to 4 weeks. Therefore, albumin-interferon may be dosed less frequently than peginterferon.

Albumin-interferon was well tolerated with no discontinuations. Adverse events were transient, and most were mild to moderate. Most common adverse events were headache (49%), fatigue (41%), injection site erythema (31%) and pyrexia (27%). Reversible neutropenia (ANC < 750) occurred in 23% of patients.

Conclusions
Several novel agents have the potential to address the unmet need for anti-HCV treatment in nonresponders to standard IFN-based therapy. Some new treatments may offer the same efficacy but reduce the dose-limiting adverse events associated with current therapies, such as ribavirin-induced hemolytic anemia. Immune modulators enhance or supplement the body’s innate immunity, resulting in the increased clearance of HCV. Antiviral agents directed against key enzymes serve to cripple HCV replication and boost the efficacy of peginterferon. Interferon alternatives, such as albumin-bound interferon, offer the potential for prolongation of half-life, and therefore, less frequent dosing. Each of these represents an important advance in the treatment of HCV infection, and findings from ongoing clinical trials of these and other agents will allow us to optimize outcomes in patients with HCV.

As previously mentioned, no novel therapy is likely to be licensed in the next few years given the protracted drug approval process, even if clinical trials progress within a reasonable time frame. Therefore, in patients with strong indications for treatment, therapy should not be deferred in the hope of being able to access alternative agents soon. Many nonresponders to standard therapy are highly motivated to participate in clinical trials of new agents and should be encouraged to do so. Two important patient groups to be included in future investigations are nonresponders, particularly those with advanced fibrosis/cirrhosis, who may not be eligible for participation in the early phase of novel drug development, and the growing population of relapers to peginterferon and ribavirin, in whom novel agents combined with standard therapy might prove particularly effective.

Figure 2. Albumin/IFN Fusion Protein and HCV RNA Reduction—Maximum HCV RNA Reduction by Dose Group

References
CME Instructions

To receive CME credit for your participation in this CME activity, please complete the following steps:

1. Read this newsletter carefully.
2. Complete the CME Posttest below, selecting the most appropriate response to each question.
3. Complete the CME Evaluation.
4. Send photocopies of the Posttest and Evaluation to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424, or fax to: 973-890-8866 by January 26, 2006. Please note that we cannot issue certificates of CME credit without both documents.

If you complete these steps and score 70% or higher, Projects In Knowledge will mail you an acknowledgment of participation within 6 weeks of receipt of your materials. If you score lower than 70%, you will be notified by mail and given another opportunity to retake the test.

Name _______________________________ Degrees/Credentials __________________

Mailing Address ______________________________________________________________________________________________

City __________________ State ________ ZIP ________________

Office Phone ____________________________ Office Fax ____________________________

E-mail _________________________________________________________________

Please select the most appropriate response to each question.

1. The biggest therapeutic limitation of ribavirin is:
   A. Dose-limiting renal toxicity
   B. Dose-limiting hepatic toxicity
   C. Dose-limiting hemolytic anemia
   D. Narrow safe dosing range

2. Which of the following is true of pegylated interferon/viramidine combination therapy?
   A. Its on-treatment antiviral activity is comparable to that of pegylated interferon/ribavirin
   B. It has similar efficacy to pegylated interferon and ribavirin in all HCV genotypes
   C. Compared with ribavirin, it is associated with a significantly lower incidence of anemia
   D. All of the above

3. The IC41 vaccine induces what type of immune response?
   A. Activation of CD4+ T cells
   B. Activation of CD8+ T cells
   C. Activation of B cells
   D. A & B only

4. Which of the following is an effect of isatoribine?
   A. Acceleration of HCV clearance
   B. Stimulation of innate immunity
   C. Promotion of localized cytokine signaling
   D. All of the above

5. Which of the following is not a feature of the albumin/IFN fusion protein?
   A. The antiviral properties of IFN
   B. The long serum half-life of albumin
   C. Dose-limiting toxicity
   D. Efficacy in patients who have failed IFN-based therapy
Pipeline Innovations in Hepatitis C Treatments

Name __________________________________________ Degrees/Credentials ______________________________

Address ___________________________________________________________________________________________________

City __________________________________________ State _______________ ZIP _______________________

Instructions: Please complete this survey, along with the CME Posttest, and mail or fax (both sides) to Projects In Knowledge, 150 Clove Road, Little Falls, NJ 07424; fax: 973-890-8866. We cannot issue CME certificates of credit without both documents.

1. Please rate the extent to which you achieved the learning objectives:

- Identify the mechanisms of action and pharmacokinetics of novel agents being evaluated for the treatment of HCV infection and relate how these may be associated with improved antiviral efficacy or improved tolerability compared with current standard anti-HCV therapy.

- Evaluate the emerging safety and efficacy data of new immune modulators, antiviral agents, and alternative interferon therapies.

- Incorporate an understanding of the timeline for drug development into a rationale for current treatment decisions.

- Counsel HCV-infected patients regarding current and future therapeutic approaches to the nonresponder population.

2. Please rate the extent to which this activity achieved the stated goal:

   The goal of Pipeline Innovations in Hepatitis C Treatments is to provide physicians with the latest clinical information and insights on novel treatments of HCV as reported from The Liver Meeting 2004.

3. Course was free from commercial bias:

   If you “Disagree” or “Strongly Disagree,” why? ........................................................................................................................................................................

4. Course was objective and independent:

5. Please rate the level of the material presented:
6. Please list any changes in your practice that you would consider making as a result of participating in this activity:

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7. Please rate your interest in self-directed or distance learning in the following formats:  

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<thead>
<tr>
<th>Format</th>
<th>Very Interested</th>
<th>Moderately Interested</th>
<th>Not Interested</th>
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<tbody>
<tr>
<td>a. Audioconference</td>
<td>❑</td>
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<td>b. Videoconference</td>
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<td>c. Enduring materials (audio CDs, videotapes, monographs)</td>
<td>❑</td>
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<td>d. Internet (online discussions with experts, educational activities)</td>
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<td>e. Multimedia (online, CD-ROM)</td>
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8. Please tell us exactly how long it took you to complete this course (circle minutes):

   Minutes: 0 15 30

9. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

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10. Follow-up:

    As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:

    ❑ Yes, I would be interested in participating in a follow-up survey.
    ❑ No, I’m not interested in participating in a follow-up survey.

11. Additional comments about this activity: ....................................................................................................................................................................................................................................................................
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Thank you for your participation.