Review

Hepatitis C Protease and Polymerase Inhibitors in Development

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ABSTRACT

Hepatitis C infection (HCV) remains a global problem and the current anti-HCV therapies available in the clinic have sustained virologic response rates (SVR) of only about 50%, especially in HCV genotype 1-infected subjects. The SVR is even lower in HIV-HCV co-infected patients, estimated at only about 30–40%. However, exciting new research is under way to find new anti-HCV therapies. Presently, efforts to develop new anti-HCV agents for HCV-infected persons who fail pegylated interferon and ribavirin-based therapies have focused on inhibitors of key HCV enzymes such as the HCV NS3 protease and the NS5B polymerase. There are two protease inhibitors, telaprevir (VX-950, Vertex) and boceprevir (SCH 503034, Schering-Plough); and three polymerase inhibitors, valopicitabine (NM283, Idenix), R1626 (Roche), and HCV-796 (Viropharma) that have advanced to late-stage clinical trials. Of these aforementioned agents, telaprevir is the most advanced in clinical development. Early trial results on efficacy, safety, and HCV drug-resistance profiles of these novel agents will be discussed in this review paper.

INTRODUCTION

HEPATITIS C VIRUS (HCV) infection affects approximately 4 million people in the United States and an estimated 170 million people worldwide.^{1,2} Approximately 250,000 of HIV-infected persons living in the United States are co-infected with HCV.² HCV infection is one of the leading causes of chronic liver disease and contributes significantly to morbidity and mortality in individuals with HIV-HCV coinfection.³ In the HIV population, HCV co-infection is highly correlated with a history of injection drug use, whereas HCV coinfection

rates are lower in other risk groups such as men who have sex with men.⁴

HCV can be divided into 6 genotypes depending on genomic sequence variation and can be further classified into subtypes (e.g., 1a or 1b). Each genotype/subtype varies in their geographical distribution and has different responses to currently available anti-HCV therapy. In the United States, genotype 1 is the most predominant, especially in HIV-HCV co-infected and the African-American population. The current standard of treatment consists of pegylated interferon- α 2 (PEG-IFN) and ribavirin (RBV). This treatment is poorly tolerated

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by patients because of its side effects and only about 50% of HCV genotype 1-infected patients achieve a sustained virologic response after treatment.⁵⁻⁸ In HIV-HCV co-infected patients, the response rate is much lower, estimated at 30-40%.⁹ Thus, there is considerable interest in the development of potent anti-HCV drugs that target specific steps of the HCV life cycle, hence the term STAT-Cs (specific targeted antiviral therapies for hepatitis C).

Many HIV clinicians now treat HCV-infected patients, and there is a need in the field to keep abreast of new anti-HCV therapies in development. Most efforts to develop new anti-HCV agents for patients who fail PEG-IFN+RBV-based therapies have focused on inhibitors of key HCV enzymes such as the HCV NS3 protease and the NS5B polymerase (an RNA-dependent RNA polymerase). Unfortunately, most of these drugs are initially evaluated in HCV-monoinfected patients, leaving the drug evaluation process for HIV-HCV co-infected patients for post-Food and Drug Administration (FDA) approval studies. This review paper will discuss the new anti-HCV drugs that target these two viral enzymes that are in late-stage clinical development and the HCV drug resistance profiles of these new agents.

NS3 PROTEASE INHIBITORS

The HCV NS3 gene encodes a serine protease and NTPase/helicase.^{10,11} The NS4A gene en-

codes a protein that serves as a cofactor for the serine protease. The NS3-NS4A complex plays an important role in the final steps of the HCV replication cycle, specifically the maturation step. In addition, the NS3-NS4A complex is believed to block the activation of interferon regulatory factor 3 (IRF-3), resulting in host immune evasion.

One of the first HCV protease inhibitors developed, BILN-2061, showed promising phase I results but was cardiotoxic to animals; thus, further development of the drug was discontinued.¹² However, there are two protease inhibitors, telaprevir (VX-950, Vertex, Cambridge MA) and boceprevir (SCH 503034, Schering-Plough, Kenilworth NJ) that have advanced to late stage Phase II trials and will be discussed in this review. The definitions of terms that are commonly used for responses to HCV treatment can be found in Table 1.

Telaprevir (VX-950)

Telaprevir (TVR) is a peptidomimetic compound that inhibits the HCV NS3-4A serine protease. This drug is at a later stage of development, in comparison with other protease and polymerase inhibitors. In an earlier Phase I trial, 34 subjects (27 prior nonresponders to Peg-IFN+RBV, and 7 HCV treatment-naïve) were randomized to receive different dosages of VX-950 or placebo for 14 days. Virologic response rates were promising with HCV RNA level decreases ranging from $-3.46 \log_{10}$ to $-4.77 \log_{10}$ IU/mL. Viral breakthrough was

TABLE 1. DEFINITIONS OF TERMS USED IN HCV THERAPY AND VIROLOGIC MONITORING

Rapid virologic response (RVR)	Undetectable HCV-RNA level at week 4 of treatment
Early virologic response (EVR)	Greater than 2 log decline from baseline HCV-RNA level at week 12 of treatment
Partial virologic response	Greater than 2 log decline from baseline HCV-RNA by week 12 but HCV-RNA level remains detectable at week 24 of treatment
Sustained virologic response (SVR)	Undetectable HCV-RNA level up to 24 weeks after the end of treatment
End of treatment response (ETR)	Undetectable HCV-RNA level at the end of treatment
Null response	Less than 2 log decrease in HCV RNA from baseline by week 12
Nonresponder	Failure to achieve undetectable HCV-RNA level at any time point during treatment
Virologic breakthrough	Initial decline in HCV RNA to undetectable level followed by return of HCV RNA levels during continued treatment
Relapse	Undetectable HCV RNA at the end of treatment but HCV RNA levels return after treatment discontinuation

noted at days 7 and 14 of dosing in the 450 mg every 8 hours and 1250 mg every 12 hours groups. In the 750 mg every 8 hours group, HCV RNA levels continued to decrease until the end of the dosing period. More importantly, 2 of the 8 subjects in this group achieved undetectable viral load (<10 IU/mL) on day 14. The most frequent side effects were headache, flatulence, diarrhea, frequent urination, dry mouth, fatigue, and dry skin and were similar across all dosage groups.¹³

At several time points, the HCV NS3 protease region was sequenced to determine the presence of drug-resistant viruses. Mutations within the NS3 gene were observed resulting in amino acid substitutions that caused low-level resistance. These changes included (1) V36M/A/L, which caused ~4-fold decreased sensitivity; (2) R155K/T/S/M, which caused ~7-fold decreased sensitivity; and (3) T54A, causing ~12-fold decreased sensitivity to the drug. Mutations that caused higher-level resistance included (1) A156V/T causing ~466-fold decreased sensitivity; and (2) double mutation with V36A/M and R155K/T causing ~781-fold decreased sensitivity to the drug. After discontinuation of the drug, the high-level resistant strains A156V/T were replaced by wild-type virus rapidly.^{14,15} *In vitro* studies have demonstrated that HCV replicons with mutations conferring resistance to telaprevir remained sensitive to IFN and RBV. A summary of HCV genes, drugs in development, and resistance mutations can be found in Table 2.

In another Phase 1 telaprevir study, 20 treatment-naïve subjects infected with HCV genotype 1 were randomized to receive either telaprevir alone ($n = 8$), PEG-IFN α -2a ($n = 4$), or telaprevir + PEG-IFN α -2a ($n = 8$) for 14 days. PEG-IFN was administered on days 1 and 8 only. The median HCV RNA decrease was $-4.0 \log_{10}$ for those who received telaprevir alone, $-1.1 \log_{10}$ for PEG-IFN α -2a alone, and $-5.5 \log_{10}$ for the combination TVR+PEG-IFN α -2a, respectively. Four of 8 patients in the combination arm achieved undetectable (<10 IU/mL) viral loads. None of the patients in this group experienced virologic breakthrough during the dosing period. No serious adverse events were reported.^{16–19}

A third Phase I study investigated the use of telaprevir in addition to the standard treatment

TABLE 2. SUMMARY OF HCV PROTEASE AND POLYMERASE INHIBITORS AND DRUG RESISTANCE MUTATIONS

Anti-HCV drugs	Resistance mutations
NS3 protease inhibitors	
Telaprevir (VX-950)	V36M/A/L R155K/T/S/M A156V/T
Boceprevir (SCH503034)	T54A A156T V170A
NS5B polymerase inhibitors	
Valopicitabine (NM283)	S282T S96T N142T
R1626	
HCV-796 (non-nucleoside)	C316Y

of PEG-IFN + RBV. Twelve treatment-naïve subjects infected with HCV genotype 1 were given PEG-IFN (180 μ g/wk subQ), RBV (1000–1200 mg/day orally), and telaprevir at 750 mg every 8 hours orally for 28 days. All 12 subjects achieved undetectable HCV RNA levels at the end of the 4-week treatment. Interestingly, early HCV genotypic analysis of patient samples prior to subjects achieving a nondetectable HCV RNA viral load revealed that some viral strains had NS3 mutations at V36M, A156V/T, and R155K/T.^{20–22}

In the most advanced trial of telaprevir, PROVE 1, a placebo-controlled Phase II study randomized 250 HCV genotype 1-infected treatment naïve subjects into four treatment groups.²³ Three groups received telaprevir (TVR) at 750 mg orally every 8 hours in addition to PEG-IFN (180 μ g/wk subQ) and RBV (1000–1200 mg/day) for 12 weeks. Depending on the treatment arm assigned, these subjects then received no further treatment, 12 weeks or 36 weeks of PEG-IFN, and RBV. The control group received the standard treatment of up to 48 weeks of PEG-IFN and RBV. Interim intent-to-treat analysis of the first 80 enrolled subjects were presented recently at the European Association for the Study of Liver Disease (EASL 2007) conference by McHutchison et al.²³ Rapid virologic response rates were 79% in the TVR triple drug arm as compared to only 11% in the control arm ($p < 0.001$). At Week 12, 70% of subjects achieved early virologic response (EVR) in the TVR triple drug arm as compared to only 39% in the control arm ($p < 0.001$). Viral breakthrough was described in 12 subjects

(7%) from the triple drug arm and 2 subjects (3%) in the control arm. Genotypic resistance testing is still in progress. Adverse events were similar across all the groups. The most common side effects were rashes and gastrointestinal complaints.

Recently, preliminary data from a planned interim analysis of subjects in arm C of the PROVE 1 study, wherein treatment-naïve subjects received TVR+PEG-IFN 2a+RBV for 12 weeks, followed by 12 weeks of treatment with PEG-IFN 2a+RBV, showed that among patients who achieved EVR and completed the 24-week treatment course, <10% of the subjects in this group experienced virologic relapse at the 12-week post-treatment follow-up.²⁴

Another ongoing randomized, multicenter placebo-controlled Phase IIb study in Europe (PROVE 2) randomized 323 treatment-naïve genotype 1 HCV-infected patients into 4 treatment groups: (A) TVR+PEG-IFN 2a+RBV for 12 weeks, (B) TVR+PEG-IFN 2a for 12 weeks (no RBV in this group), (C) TVR+PEG-IFN 2a+RBV for 12 weeks followed by 12 weeks of PEG-IFN+RBV, and (D) PEG-IFN 2a + RBV for 48 weeks (control arm). At the most recent American Association of the Study of Liver Diseases (AASLD), EVR rates were reported at 79% in the TVR+PEG-IFN+RBV arms ($p < 0.001$), 63% in the TVR+PEG-IFN arm, and 43% in the control arm. At the end of 12 weeks of treatment, virologic breakthrough was observed in 4% of those in the TVR+PEG-IFN+RBV arms versus 24% in the TVR+PEG-IFN without RBV arm, suggesting the importance of RBV in the maintenance of viral suppression. Drug-resistant mutations including V36M, R155K, A156S/T, and T54A were reported.²⁵

Boceprevir (SCH503034)

Boceprevir, a carboxamide-based compound, is also an oral HCV NS3 protease inhibitor. In a randomized, double-blind placebo-controlled phase I study, HCV genotype 1 infected nonresponders to PEG-IFN+RBV were randomized to receive boceprevir at either 100 mg every 12 hours, 200 mg every 12 hours, 400 mg every 12 hours, 400 mg every 8 hours versus placebo orally for 14 days. HCV

RNA levels decreased $-2.16 \log_{10}$ IU/mL (range of -1.1 to -2.7) in the 400 mg every 8 hour group. Side effects were minimal and were similar among all groups.²⁶

In vitro studies have demonstrated synergistic antiviral activity when PEG-IFN was added to boceprevir. This led to a multicenter, open-label, 3-way crossover study wherein 26 HCV genotype 1 infected PEG-IFN+RBV nonresponders received in random sequence: (A) 200 mg or 400 mg boceprevir monotherapy for 7 days; (B) PEG-IFN α -2b ($1.5 \mu\text{g/kg}$ weekly) monotherapy for 14 days; and (C) boceprevir + PEG-IFN α -2b for 14 days.^{27,28} There was a 2-week washout period between each intervention. HCV RNA levels decreased by -1.08 ± 0.22 and $-1.61 \pm 0.21 \log_{10}$ IU/mL with 200 mg and 400 mg boceprevir monotherapy, respectively, versus -1.08 ± 0.22 and $-1.26 \pm 0.20 \log_{10}$ IU/mL for PEG-IFN alone in the 200 mg and 400 mg cohorts. With the combination treatment, the reduction in HCV RNA levels were $-2.45 \pm 0.22 \log_{10}$ IU/mL and $-2.88 \pm 0.22 \log_{10}$ IU/mL in the 200 mg and 400 mg plus PEG-IFN cohorts. Except for a slightly higher incidence of headache, rigor, and myalgia in the combination therapy group, the drug was well tolerated and adverse events were similar.^{27,28} *In vitro* studies have demonstrated mutations of T54A causing ~6-fold decreased sensitivity, A156T causing ~80-fold decreased sensitivity, and V170A causing ~16-fold decreased sensitivity to boceprevir.^{15,29,30}

A Phase II dose-finding clinical trial in HCV genotype 1 nonresponders is under way. The study will evaluate treatment with boceprevir in combination with PEG-IFN α -2b with and without RBV. Other studies being planned include a higher dosage of boceprevir (up to 800 mg every 8 hours) in combination with PEG-IFN and RBV. The drug will also be evaluated in treatment-naïve patients, HIV-HCV co-infected populations, and liver transplant recipients.

NS5B polymerase inhibitors

The NS5B polymerase enzyme is an RNA-dependent RNA polymerase that plays an essential role in HCV protein translation and synthesis, leading to viral replication. It displays a

finger/palm/thumb motif with a number of interaction sites that are potential targets for drugs in development.³¹ There are currently two nucleoside analogs (valopicitabine; Idenix, Cambridge, MA, and R1626; Roche, Basel, Switzerland) and one non-nucleoside analog (HCV-796; ViroPharma, Exton, PA) in Phase II trials. Another nucleoside polymerase inhibitor, R7128 (Pharmasset, Princeton, NJ), is in Phase I trials; however, because of limited data on efficacy and safety, trial results will not be discussed here.

Valopicitabine (NM283)

Valopicitabine is a nucleoside analog and the orally bioavailable prodrug of NM107 that competitively inhibits NS5B polymerase, causing chain termination. Godofsky et al. conducted a Phase I study wherein subjects received either 50 mg, 100 mg, 200 mg, 400 mg, and 800 mg of NM283 orally.³² The 800 mg group showed the highest antiviral efficacy, with a mean decrease in HCV RNA levels of $-1.21 \log_{10}$ IU/mL. There was a slightly higher incidence of nausea and vomiting at dosages of more than 400 mg/day.³²

In vitro studies have shown enhanced antiviral activity when NM283 was combined with PEG-IFN α . In a 12-week multicenter Phase II study, 30 treatment-naïve HCV genotype 1 infected subjects received escalating doses of NM283 (400 mg $\rightarrow$ 600 mg $\rightarrow$ 800 mg) over the first 8 days. At Day 9, 14 patients continued on NM283 monotherapy, while the remaining 16 were started on PEG-IFN α -2b at 1.0 μ g/kg weekly. HCV RNA levels decreased $-3.01 \log_{10}$ IU/mL in the NM283 + PEG-IFN arm as compared to $-0.87 \log_{10}$ IU/mL in the NM283 monotherapy arm.³³

In a phase IIb study, HCV genotype 1 infected treatment-naïve subjects with HCV RNA $\geq 5 \log$ IU/mL were randomized to receive any of the following 5 treatments: (A) PEG-IFN for 4 weeks then PEG-IFN + NM-283 800 mg/day thereafter; (B) NM283 200 mg/day for 1 week then NM283 200 mg/day + PEG-IFN; (C) NM283 400 mg/day increased to 800 mg/day within the first week then NM283 800 mg/day + PEG-IFN; (D) NM283 800 mg/day for 1 week then NM283 800 mg/day + PEG-

IFN; and (E) NM283 800 mg/day + PEG-IFN. PEG-IFN was dosed at 180 μ g weekly starting at Day 8 for groups A through D or since Day 1 for group E. In this study, 89–96% of subjects demonstrated EVR. However, gastrointestinal (GI) -related adverse events were more frequent in the high-dose NM 283 + PEG-IFN group, resulting in 14% of patients stopping therapy prior to completing 12-week treatment. This led to a protocol amendment wherein the NM283 dosage was reduced to 200 mg/day or 400 mg/day after 14–22 weeks of treatment. Continued antiviral efficacy was observed across all treatment groups. At weeks 24 and 36, HCV viral load reduction was reported at -3.8 to $-4.5 \log_{10}$ IU/mL from baseline. Undetectable RNA levels were seen in 50–70% of the subjects by week 36. At week 48 (end-of-treatment response), antiviral activity was maintained but the viral load reductions were somewhat similar: $-4.02 \log_{10}$ IU/mL in the 200 mg NM283 + PEG-IFN arm and $-3.94 \log_{10}$ IU/mL in the higher dose arm + PEG-IFN.^{34,35}

In another phase IIb study conducted by O'Brien et al.,³⁶ 178 HCV genotype 1 patients who were treatment nonresponders to PEG+IFN but had compensated liver disease were randomized to either of the 5 treatment arms: NM283 800 mg alone ($n = 21$), different NM283 dosing (400 mg/day; 800 mg/day or dose-ramping 400–800 mg/day followed by 800 mg/day) + PEG-IFN ($n = 41$ each group) or retreatment with PEG-IFN + RBV ($n = 34$). PEG-IFN was dosed at 180 μ g weekly and RBV was dosed at 1000–1200 mg/day. At 12 weeks, the mean HCV RNA reductions were $-2.5 \log_{10}$ IU/mL to $-2.8 \log_{10}$ IU/mL in the 800 mg NM283 + PEG-IFN group as compared to $-1.9 \log_{10}$ IU/mL in the PEG-IFN plus RBV retreatment arm ($p = 0.01$). There was a higher proportion of patients achieving an EVR, with 63–71% versus 41% in the NM283 higher dose arms and PEG-IFN + RBV retreatment arm, respectively. Because of major GI side effects (nausea and vomiting), valopicitabine dose was reduced by protocol amendment to 400 mg/day after more than 40 weeks of treatment. Patients who received combination therapy were observed to have a HCV RNA reduction of -3.08 to $-3.14 \log_{10}$ IU/mL, as compared to

$-2.29 \log_{10}$ IU/mL in the PEG-IFN + RBV retreatment arm (not statistically significant, $p = 0.06$).^{36,37} Final SVR data are anticipated soon.

No *in vivo* resistance data are available as of yet; however, sequence analysis of the HCV NS5B gene of drug-resistant replicons have demonstrated a single mutation within the NS5B gene, resulting in an amino acid substitution serine 282 to threonine (S282T), which can cause a ~ 5 to 10-fold decreased sensitivity to NM-283.^{15,38,39} *In vitro* studies done by Bichko et al. showed that HCV replicons with NS3 protease inhibitor mutations including R155K, A156T, D168A, D168V, and D168Y were fully sensitive to NM107.³⁸ In another study presented recently at EASL 2007, the combination of SCH503034 and NM107 showed enhanced anti-replicon activity with no cross-resistance,⁴⁰ thus supporting the possibility of combination therapy of NS3 protease inhibitors and NM283 in HCV-infected patients.

Unfortunately, because of the overall risk/benefit profile of subjects undergoing clinical trials, further development of the drug has been temporarily placed on hold by the company and the FDA.⁴¹

R1626 (Roche)

R1626 is nucleoside analog that inhibits the NS5B polymerase enzyme. It is the prodrug of R1479 (4'-acidocytidine), which selectively inhibits the HCV polymerase. In a phase I study by Roberts et al., treatment-naïve HCV genotype 1 infected subjects were randomized to receive R1626 monotherapy at 500 mg, or 1500 mg, or 3000 mg, or 4500 mg, or placebo orally every 12 hours for 14 days. Maximal HCV RNA reduction was noted with the higher doses, $-2.6 \log_{10}$ and $-3.7 \log_{10}$ for the 3000 mg and 4500 mg arms, respectively. There was significant decline in the HCV-RNA levels in 8 of 9 subjects, reaching less than 600 IU/mL and 5 of 9 subjects had less than 50 IU/mL HCV-RNA at the end of the 14-day dosing period. Side effects were common in the 4500 mg group, and included headache, nausea, and diarrhea. Anemia was also observed in the higher dose groups, with a drop in hemoglobin level of almost 1 g/dL, but this was reversible after

discontinuation of the drug. None of the subjects had to withdraw treatment because of safety reasons.⁴²

Viral breakthrough was reported in 3 of 9 subjects from the 500 mg arm and no phenotypic resistance has been reported yet. Other *in vitro* studies have shown mutations causing amino acid substitutions at serine 96 to threonine (S96T) and asparagine 142 to threonine (N142T). In another study, R1479 was shown to be unaffected by the S282T mutation, suggesting that *in vitro* there is no cross-resistance between R1479 and valopicitabine.⁴³ A randomized, double-blind phase II study of R1626 in combination with PEG-IFN with and without RBV is ongoing in HCV genotype 1 treatment-naïve subjects.

HCV-796 (Viropharma/Wyeth)

HCV-796 is a non-nucleoside polymerase inhibitor that has been shown to be effective in early clinical trials. In a phase I, randomized, double-blind, placebo-controlled study, HCV treatment-naïve subjects (72% genotype 1, genotypes 2–4 also represented) received HCV-796 alone at either 50 mg, 250 mg, 500 mg, 1000 mg, 1500 mg versus placebo orally every 12 hours for 14 days' duration. The maximal decrease in HCV RNA levels was observed in the 1000 mg and 1500 mg arms ($-1.4 \log_{10}$ IU/mL). Approximately 85% of subjects achieved a 1-log drop and 30% of subjects had a 2-log drop in their viral loads; however, there was viral breakthrough reported in some subjects. No serious adverse events were reported. A mild hyperbilirubinemia was observed by the first week of therapy, but this eventually resolved.⁴⁴

Villano et al. determined the NS5B genetic sequence in 42 HCV genotype 1 infected subjects and found that of 21 patients (50%) who experienced viral breakthrough, 11 subjects had a C316Y mutation, which conferred resistance to HCV-796, but this viral variant did not affect IFN- α and RBV susceptibility, suggesting that there is no cross-resistance between HCV-796 and IFN- α + RBV.⁴⁵

HCV-796 has also been studied in combination with PEG-IFN in a phase 1b double-blind, placebo-controlled study wherein HCV-infected treatment-naïve subjects (64% genotype

1) were randomized in sequential dose cohorts to receive HCV-796 at either 100 mg, 250 mg, 500 mg, 1000 mg, or placebo orally every 12 hours for 14 days. PEG-IFN at 1.5 $\mu\text{g/kg/dose}$ was administered to all subjects on Day -1 (1 day before the start of HCV-796/placebo) and Day 7. HCV-RNA levels decreased $-3.4 \log_{10}$ IU/mL in the combination therapy group as compared to $-1.6 \log_{10}$ IU/mL in the PEG-IFN monotherapy group. A subgroup analysis of genotype 1 subjects showed a mean HCV-RNA reduction of -2.6 to $-3.2 \log_{10}$ IU/mL in the combination groups as compared to $-1.2 \log_{10}$ IU/mL for PEG-IFN alone.⁴⁶ In non-genotype 1 patients, the response rate was higher (-3.5 to $-4.8 \log_{10}$ IU/mL in the combination arm versus $-2.6 \log_{10}$ IU/mL in the PEG-IFN arm). Side effects included headache, chills, rash, and myalgia, which are commonly related to interferon use.⁴⁶ There are currently no data available regarding the emergence of drug-resistant mutations among these subjects.

In a randomized open-label phase II study of HCV-796 in combination with PEG-IFN α -2b and RBV in treatment-naïve subjects and treatment nonresponders, there were three dosing groups with at least 74 patients per group: (A) treatment-naïve subjects receiving PEG-IFN+RBV (control group); (B) treatment-naïve subjects receiving PEG-IFN+RBV and 500 mg HCV-796 every 12 hours; and (C) nonresponders receiving PEG-IFN+RBV and 500 mg HCV-796 every 12 hours. All patients were to receive treatment up to 48 weeks and will be followed for a further 24-week period. Recently, the developers of HCV-796 placed a hold on the development of this compound because elevated liver enzyme levels were noted in $\sim 8\%$ patients after 8 weeks or more of therapy with HCV-796 with PEG-IFN+RBV.⁴⁷ At this time, it is unknown whether HCV-796 will be developed further.

There are other anti-HCV protease and polymerase inhibitors in early stages of development, as well as α -glucosidase inhibitors, modified cyclophilins, viral entry inhibitors, antisense molecules, ribozymes, and small interfering RNAs that are in preclinical trials.¹⁹ An antiparasitic drug, nitazoxanide, has also been studied for the treatment of chronic hepatitis C, and results of an early Phase II trial

in genotype 4-infected subjects have shown that the addition of nitazoxanide to PEG-IFN+RBV improved SVR rates in treatment-naïve subjects infected with genotype 4 strains.⁴⁸ It remains questionable as to which drugs in early development will eventually advance to later-stage clinical trials.

CONCLUSION

Many HIV clinicians have incorporated the treatment of HCV-infected and HIV-HCV co-infected patients into their practices. Unfortunately, they are now faced with HCV-infected patients who have failed standard anti-HCV therapies. Exciting new research is under way to find suitable alternatives to PEG-IFN+RBV-based anti-HCV therapies. As with HIV drug development, protease inhibitors, nucleoside analogs, and non-nucleoside polymerase inhibitors are being investigated to combat HCV. However, to successfully develop these agents, the field must overcome the serious problem of drug safety, tolerance, and efficacy as well as the emergence of drug-resistant HCV strains.³⁵⁻⁴³ Early clinical trial data have shown that many of the new HCV protease and polymerase inhibitors have enhanced activity when combined with PEG-IFN and/or RBV. Furthermore, these trial results suggest that PEG-IFN will remain an integral component of HCV therapy for the foreseeable future. However, as with any new therapeutic drug class, many promising agents may fail to make it to the clinic because of toxicity issues, especially when combined with antiretroviral therapy for HIV-HCV co-infected patients. In the relatively near future, new anti-HCV drug combinations such as protease and polymerase inhibitors with or without PEG-IFN and RBV could be available in the clinic if ongoing clinical trials continue to show efficacious and promising results.

ACKNOWLEDGMENTS

GLY is supported by T-32 NIH Yale ID training grant and BMS Virology Fellows program. MJK hepatitis C research is supported by the

Veterans Administration and the National Institute of Diabetes and Digestive Diseases R21 DK071669-01 (Kozal PI). In addition, MJK has received royalties from a patent owned by Stanford University for some HIV genotype resistance tests. MJK is the local primary investigator on 3 Merck HIV-1 Integrase Inhibitor studies, and studies sponsored by Tibotec and Boehringer-Ingelheim. In the last 12 months, M.J.K. has received speaker fees, including reimbursement for travel and accommodation expenses from Abbott and 454 Life Sciences/Roche. In the last 12 months, Dr. Kozal has served as a consultant for HIV and Hepatitis C research for Merck and Schering-Plough Research Institute and on HIV resistance assays for Stanford University.

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