



CIFN 18 µg once daily.<sup>19</sup> After 16 weeks, both treatment groups received CIFN 9 µg once daily for 32–72 weeks. RBV was initiated after the first 4 weeks of treatment at a dosage of 11 mg/kg/day. Treatment was continued until patients were HCV RNA negative for at least 48 weeks (up to 72 weeks maximum). Patients were assessed 24 weeks after the end of treatment for SVR.

There were 30 patients in each treatment group. At 24 weeks of therapy, 40% of patients in the CIFN 9 µg group and 47% of patients in the CIFN 27/18/9 µg group were negative for HCV RNA. At the end of treatment, these values were 43% and 50%, respectively. SVR was achieved in 23% of patients in the CIFN 9 µg group and in 27% of patients in the CIFN 27/18/9 µg group.

The rates of adverse and serious adverse events in this trial were comparable to those seen with standard combination therapy. Two patients in the high dose group experienced grade IV neutropenia (ANC < 500/µL), and 1 patient experienced grade III/IV thrombocytopenia. No growth factors were used in this trial. Discontinuation and dose reduction rates were also similar to those observed with standard interferon and ribavirin therapy. The CIFN 9 µg and CIFN 27/18/9 µg cohorts had discontinuation rates of 3% and 10%, and dose reduction rates of 10% and 23%, respectively.

Leevy and colleagues conducted a retrospective review to evaluate the efficacy of CIFN in PEG-IFN plus RBV nonresponders.<sup>20,21</sup> All patients had previously received PEG-IFN α-2b 1.5 µg/kg once weekly plus weight-based RBV (1000–1200 mg/day) for 12 weeks. Responders continued with the PEG-IFN α-2b-based regimen. Without a washout period, nonresponders (defined as not achieving at least a 2-log<sub>10</sub> decline in HCV RNA) were started on CIFN 15 µg once daily plus weight-based RBV for 12 weeks. The CIFN dose was reduced to 15 µg TIW for the subsequent 36 weeks.

Among all 137 patients, on-treatment responses at weeks 12, 24, and at the end of therapy (48 weeks) were seen in 23%, 31%, and 43%, respectively (see Figure 1). The SVR rate among all patients was 37%. There were differences between African American (n = 45) and non-African American patients (n = 92). On-treatment

responses at weeks 12, 24, and 48 were 13%, 24%, and 31%, respectively, among African Americans. The corresponding values for non-African Americans were 28%, 35%, and 48%. SVR rates were also lower for African Americans than for non-African Americans, although the difference did not reach statistical significance (27% vs 41%, P = 0.09). Therapy was well tolerated in all patients; flu-like symptoms and fatigue were reported in most patients, but no patients discontinued therapy. Sixteen percent (22 patients) had ANC drop below 750/mL, and required growth factors.

Given that approximately 14% of patients respond to retreatment with pegylated interferon that have failed on standard IFN and RBV, and preliminary studies suggesting that daily dosing of CIFN plus RBV can achieve improved outcomes, the DIRECT trial (**D**aily-dose **C**onsensus **I**nterferon and **R**ibavirin: **E**fficacy of **C**ombined **T**herapy) was designed to study the efficacy and safety of daily CIFN plus RBV in patients not responding to PEG-IFN plus RBV therapy. DIRECT is a Phase III, randomized (1:1:1), open-label research study to determine the SVR rate of combination therapy with daily CIFN plus RBV compared to no treatment in HCV-infected patients in this nonresponder population. Approximately 510 patients at 41 sites in the United States have been randomized to receive CIFN 15 µg plus RBV daily for 48 weeks, CIFN 9 µg plus RBV daily for 48 weeks, or no treatment for 24 weeks (may be eligible for randomization to a rollover study).

Included patients will have documented viral nonresponse to past treatment with PEG-IFN α-2a or 2b plus RBV, defined as a

less than a 2-log<sub>10</sub> reduction in HCV RNA from baseline at any time between 12 and 24 weeks of therapy or detectable HCV RNA at end-of-treatment (EOT), after completing at least 24 weeks of initial therapy. Secondary endpoints in this study include evaluating the safety and tolerability of CIFN plus RBV compared to no treatment in HCV-infected patients who are nonresponders to previous PEG-IFN alfa plus RBV therapy.

**CONSENSUS INTERFERON PLUS INTERFERON GAMMA-1b**

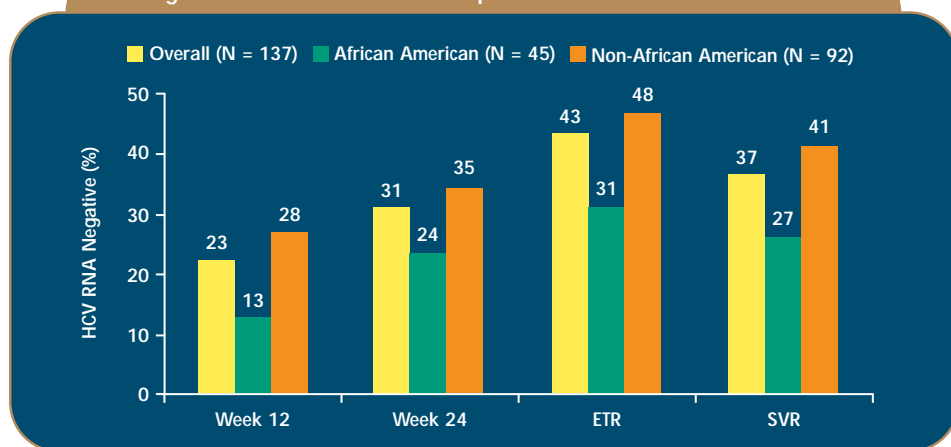
A recent trial evaluated the response to 48 weeks of CIFN 15 µg daily with IFN γ-1b 50 µg 3 times per week in PEG-IFN α-2a plus RBV nonresponders.<sup>22,23</sup> The combination of CIFN and IFN γ-1b has demonstrated strong synergistic antiviral and immunomodulatory effects in preclinical models of HCV.<sup>24</sup> In this review, 50 patients received CIFN plus IFN γ-1b for 48 weeks after failing to achieve a ≥ 2-log<sub>10</sub> drop in HCV RNA with 12 weeks of PEG-IFN α-2a plus RBV.

The EVR (12 weeks), EOT (48 weeks), and SVR in this cohort were 40%, 46%, and 34% respectively. Twenty-six percent (13/50) required filgrastim for ANC < 750/mL. Of note, the mean hemoglobin level at the start of CIFN plus IFN γ-1b therapy was 11.5 g/dL, which recovered to normal by week 8 without the use of erythropoietin. This regimen is now being evaluated in a larger cohort of HCV nonresponder patients.

**MAINTENANCE PEGYLATED INTERFERON**

It is well established that patients with chronic hepatitis C who achieve an SVR also have improvements in hepatic histology and a decrease in the risk for

Figure 1. PEG-IFN + RBV Nonresponders: CIFN Treatment Results<sup>21</sup>



hepatocellular carcinoma (HCC). In addition, it has been observed that a portion of patients who are nonresponders also demonstrate improvements in histology.<sup>25,26</sup> The effect on histology is likely related to a reduction in hepatic inflammation. Thus, it is hypothesized that continuous maintenance interferon therapy has the potential to slow progression of chronic HCV, even in the presence of persistent viremia. On the other hand, a recent review of treatment options for patients who failed to achieve an SVR suggests that PEG-IFN maintenance may not affect the natural progression of chronic HCV, particularly in patients with advanced fibrosis or cirrhosis.<sup>27</sup>

Currently, there are 3 ongoing trials designed to evaluate the efficacy of long-term maintenance therapy with low-dose weekly regimens of PEG-IFN. These studies include the HALT-C study (PEG-IFN  $\alpha$ -2a, 90  $\mu$ g/week), the COPILOT study (PEG-IFN  $\alpha$ -2b, 0.5  $\mu$ g/kg/week), and the EPIC study (PEG-IFN  $\alpha$ -2b, 0.5  $\mu$ g/kg/week).<sup>28</sup>

Preliminary results from COPILOT, comparing maintenance therapy with PEG-IFN  $\alpha$ -2b 0.5  $\mu$ g/kg/week with colchicine 0.6 mg twice daily in patients with HCV and advanced fibrosis (Ishak > 3) who have failed prior IFN-based therapies, have been presented. At the 1-year analysis, there was no significant difference between the PEG-IFN and colchicine groups for the decline in ALT (40 points vs 42 points), AFP (no change for either group), and HCV RNA level (1 log<sub>10</sub> decline in 90% of patients vs no change;  $P = 0.06$ ).<sup>29</sup>

At the 2-year analysis, 534 patients had been enrolled. Maintenance PEG-IFN therapy was found to be associated with a significant reduction in the incidence of variceal hemorrhage compared to colchicine (1 vs 9 episodes, respectively). However, there was no reduction in the incidence of other outcome measures (compared with colchicine) including, liver failure, the development of HCC, the need for liver transplantation, and death.<sup>27,30</sup> A subanalysis of 132 patients (66 PEG-IFN and 66 colchicine) from the COPILOT cohort having had baseline and repeat endoscopy at 2 years evaluated the role of portal hypertension on clinical outcomes of maintenance therapy and the role of maintenance PEG-IFN on portal pressure.<sup>31</sup> Investigators concluded that although maintenance therapy may retard the development of varices, reduce portal

pressure, and prevent variceal hemorrhage and complications of portal hypertension compared to colchicine, continued use of PEG-IFN in a maintenance regimen may have little effect on the prevention or development of liver disease.

#### FUTURE DIRECTIONS IN HCV THERAPEUTICS

Because of the large number of patients who are nonresponders to currently available anti-HCV agents, the development of new therapeutic options is crucial. Many agents, including new formulations and dosages of IFNs, RBV analogs, immune modulators, antifibrotic agents, and direct antiviral therapies, are under active investigation for the treatment of HCV infection.

Immune modulatory drugs currently undergoing evaluation in Phase III trials include: C1FN (daily dose); virmidine, a prodrug of RBV with a potentially more favorable toxicity profile compared to the parent drug; and thymosin alpha-1, which augments T-cell function. IP 501, an antifibrotic agent formerly in Phase III trials, has been discontinued.<sup>32,33</sup>

With an increased understanding of the HCV genome and life cycle and the identification of a number of potential new targets for therapy, several directed antiviral agents, with a wide range of mechanisms of action, are under investigation.<sup>34</sup> The nonstructural proteins in the HCV genome encode for several enzymes (eg, proteases and polymerases) that are vital for viral replication. In particular, agents that inhibit the HCV protease and polymerase are promising new antiviral agents. Other potential agents include vaccines and antisense oligonucleotides.

Despite this active anti-HCV research, the drug development process remains long and costly. Drug development begins with drug discovery and preclinical (ie, in vitro and animal) studies. This is followed by successive clinical phases (Phases I–III), a new drug application (NDA) to the Food and Drug Administration (FDA), and subsequent approval. The development process takes an average of 7.5 years from the start of clinical testing to FDA approval. Notably, there is a very high attrition rate of drugs in the development process. The large majority of drugs that enter the development process are terminated at some point during the process.<sup>35</sup>

Ultimately, delays and pitfalls in the drug pipeline make waiting for new and improved agents a poor option for many HCV-infected patients. The sequelae of long-term untreated HCV infection, including cirrhosis, liver failure, and HCC, are a great burden on patients and the health care system and are associated with high mortality rates. Thus, patients who have failed a course of treatment with PEG-IFN and RBV and are appropriate candidates for retreatment may realize great benefit from a trial of currently available agents directed toward eradicating the virus.

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