The current best therapy for treatment of chronic hepatitis C virus (HCV) infection is a combination of peginterferon alfa (PEG-IFN) and ribavirin (RBV). There are two U.S. FDA-approved combinations, PEG-IFN-alfa-2a and RBV, and PEG-IFN-alfa-2b and RBV. Each combination produces sustained virologic response (SVR) rates of about 55%, with rates of SVR about 42-52% among genotype 1-infected persons, and in excess of 80% among patients with genotype 2 or 3 HCV (1-3).

While over half of eligible patients experience a desirable outcome, nearly half do not. These patients will either fail to clear virus (nonresponders) by week 24 of therapy, which explains most cases of treatment failure, or initially clear virus during therapy, but experience relapse following cessation of treatment (relapse). Rarely, a patient will develop detectable viral RNA after initial clearance, despite continuation of therapy. These so-called breakthroughs only occur rarely. There is increasing appreciation of the factors that contribute to these less favorable outcomes. These fall into (1) virally-determined factors; (2) host factors; and (3) treatment-related factors. This monograph will review these factors and explore current data regarding possible strategies to overcome nonresponse.

**Viral Factors**

*Genotype* is the most important determinant of antiviral response, since those patients harboring genotype 2 and 3 HCV can expect an excellent SVR rate with a briefer requirement for PEG-IFN and RBV, in contrast to those persons with genotype 1 infection. Other viral factors that contribute to nonresponse include *high viral load* (>800,000 IU/mL) and increased sequence variability (4).

It is important to point out that all HCV isolates thus far characterized in vitro have proved sensitive to the actions of IFN. However, a variety of HCV gene products have been shown to *block endogenous IFN induction, signaling, or effector gene function*. These include HCV core, NS3/4A, and NS5A (reviewed in (5)). The best example of this is the action of the HCV NS3/4A serine protease, which cleaves the host IPS-1/Cardif protein, leading to decreased interferon regulatory factor 3 phosphorylation, and diminished production of endogenous interferon. The use of NS3/4A inhibitors blocks this cleavage and can rescue the endogenous interferon response in replicon studies. It has therefore been suggested that this class of agents may be capable of anti-HCV activity through dual mechanisms of action by not only blocking the viral lifecycle but also by rescuing interferon production and action. This inhibitory function of viral proteins on innate antiviral immunity may be a strong contributor not only to the persistence of
infection but also to the limited observed response rate to IFN-based therapy in vivo.

Host Factors

Historically, higher age, hepatic fibrosis, body mass index, and hepatic steatosis have adversely impacted SVR rates. More recently, race has emerged as an important determinant of outcome. A recently concluded NIH trial (Virahep-C) of PEG-IFN and RBV regimens given to African-American and Caucasian patients with genotype 1 HCV demonstrated that African-Americans (AA) respond nearly twice as poorly as their Caucasian (CA) counterparts (52% vs. 28%), even when correcting for other factors such as age, BMI, medication adherence and disease stage (6). Subsequent work has revealed that the chief determinant of this limited response in AA populations is the presence of elevated insulin resistance, which may itself impair IFN signaling (7). Studies of gene expression patterns from liver tissue and peripheral blood mononuclear cells have shown that induction of IFN-stimulated genes (ISGs) is higher among nonresponders than in responders (8). While at one level counterintuitive, these findings suggest that the activation of ISGs occurs in response to a downstream, functional block. This block(s), more frequent among AAs than in CAs, remains to be fully characterized. Genetic studies are ongoing, but no distinguishing polymorphisms in obvious ISGs have thus far been identified in AAs.

Treatment Factors

In addition to the viral and host factors, there are patient-specific factors that impact SVR rates within a given demographic or viral subgroup. These include the receipt of higher number of PEG-IFN and RBV doses. Findings from the lead-in phase of the Hepatitis Antiviral Long-Term Therapy to Prevent Complications of Hepatitis C (HALT-C) Trial, which is examining the value of PEG-IFN-α-2a for the management of persons who failed to clear virus with conventional PEG-IFN and RBV treatment, have shown that reducing the PEG-IFN dose to less than 80% during the first 20 weeks of re-treatment reduced end of treatment and sustained virologic response. In contrast, reducing RBV dose did not affect either on-treatment virologic response (VR) or SVR as long as patients remained on full-dose PEG-IFN. Discontinuing RBV prematurely was associated with a marked drop-off in on-treatment VR and SVR (9).

Strategies to Improve Response Rates in Nonresponders or Relapsers to PEG-IFN and RBV

At present, there are no clear guidelines for the management of the patient who experiences nonresponse or relapse following a full course of PEG-IFN and RBV. Based on available data, options will include retreatment with higher doses or different types of IFN, maintenance therapy with PEG-IFN, and treatment using PEG-IFN, RBV and specifically targeted antiviral therapy for HCV (STAT-C).

1. Retreatment of Relapsers

For relapers who achieve initial and end-of-treatment viral clearance on a course of PEG-IFN and RBV, but for whom HCV RNA returns in the 24-week followup period, there is evidence that these persons may harbor very low quantities of HCV RNA as detected by highly sensitive qualitative RT-PCR assays. In this regard,
relapsers could be more realistically viewed on a continuum with nonresponders. Data from modeling studies suggest that the duration of undetectable HCV RNA is deterministic of the ultimate ability to achieve SVR. For genotype 1 infection, it has been proposed that an effective minimum duration of viral clearance using a qualitative RT-PCR assay (LLD <50 IU/mL) is about 36 weeks (10). Support for this concept came from two studies in genotype 1 patients that extended PEG-IFN and RBV therapy to 72 weeks and found significantly higher SVR rates among treatment-naive genotype 1 patients who failed to achieve rapid virologic response (RVR, loss of detectable HCV RNA by qualitative assay by week 4 of therapy) or week 12 HCV RNA clearance (11,12) compared to those receiving 48 weeks of therapy.

While no randomized study has examined the efficacy of extended PEG-IFN and RBV treatment for PEG-IFN + RBV relapsers, on the basis of these data, it would appear reasonable to extend PEG-IFN and RBV therapy to 72 weeks, especially among those patients who failed to achieve RVR or week 12 clearance but who clear HCV RNA by week 24.

2. Retreatment of Nonresponders with Differing IFN Regimens

There are few studies that have examined the efficacy of retreatment of PEG-IFN and RBV nonresponders (defined as failure to achieve EVR (greater than 2 log drop in HCV RNA or clearance at week 12 of treatment) or failure to clear HCV RNA by qualitative assay by week 24 of treatment).

One of these, the REPEAT study, was designed to assess the efficacy of a course of PEG-IFN-α-2a + RBV following nonresponse to a prior course of PEG-IFN-α-2b. Nine hundred fifty PEG-IFN-α-2b nonresponders were randomized to receive either PEG-IFN-α-2a 180 mcg weekly for 48 or 72 weeks or a larger induction dose (360 mcg weekly) for 12 weeks followed by 36 or 60 weeks of 180 mcg weekly. All arms also received weight-based (1000-1200 mg/d) RBV. An interim analysis found that patients in the induction dose arms had a higher likelihood of achieving week 12 EVR compared to those receiving standard PEG-IFN (62 vs. 45%, p<0.0001). Despite these encouraging early response data among prior PEG-IFN and RBV nonresponders, followup data are required to determine whether this translates into improved end-of-treatment response (ETR) and SVR rates.

Other IFNs currently under study in nonresponders include consensus interferon alfa (interferon alfacon) and conjugated albumin interferon alfa-2b. In a small pilot study, 24 patients who failed to respond (12 pts) or relapsed (12 pts) to PEG-IFN-α-2b + RBV were treated with IFN alfacon (9 mcg 5 times weekly) for 36 weeks. SVR was seen in 33% of prior nonresponders and 42% of prior relapsers. These and other data led to the design of the DIRECT trial, a multicenter trial of PEG-IFN + RBV nonresponders who were randomized to receive either IFN alfacon 9 mcg daily or 15 mcg daily combined with RBV 1000-1200 mg daily. An interim analysis of this trial showed that 22% of patients in the 9 mcg and 25% in the 15 mcg group experienced ETR at week 48 (14). These data suggest that SVR rates will be modest.

IFN-α-2b conjugated with albumin takes on the longer half-life of albumin and permits dosing every other week. Albumin-IFN has been studied in a phase II study of genotype 1 patients who failed to respond to prior IFN based regimens. Subjects were treated with wither 900 mcg or 1200 mcg every 2 weeks with weight-based RBV. The overall SVR rate was 21% in the pooled albumin-IFN treatment groups. The SVR rate among patients who had failed to respond to prior PEG-IFN and RBV based therapy was 13% (15).

Collectively, these data suggest that retreatment of prior PEG-IFN and RBV nonresponders with higher doses or alternative IFNs will not produce dramatically improved SVR rates.
3. Maintenance Trials

Based on the rationale that prior courses of standard IFN produced improved liver histology even among patients who did not achieve SVR (16), 3 large trials of long-term PEG-IFN therapy to slow fibrosis progression among persons with advanced HCV liver disease who are nonresponders to PEG-IFN and RBV are ongoing. These include the CoPILOT, HALT-C and EPIC3 trials.

The CoPILOT study is examining low-dose PEG-IFN-α-2b (0.5 mcg/kg/wk) compared to colchicines in 534 patients with cirrhosis and portal hypertension who had previously failed IFN-based treatment. An interim analysis at 2 years found that the PEG-IFN was associated with decreased rates of variceal hemorrhage compared to colchicine (17). Study data are currently being analyzed.

The NIH-supported HALT-C trial enrolled 1050 patients with bridging fibrosis or cirrhosis who failed to experience response to a lead-in phase of PEG-IFN-α-2a and RBV 1000-1200 mg/d. Subjects were randomized to receive either PEG-IFN-α-2a 90 mcg/week or observation for 3.5 years. Endpoints include fibrosis progression, liver failure, HCC, and death. Study data are expected to be analyzed late in 2007.

The EPIC3 trial also took over 1800 patients with HCV and fibrosis and offered a lead-in phase of PEG-IFN-α-2b 1.5 mcg/kg/wk + RBV 800-1400 mg/d. Nonresponders were randomized to receive long-term maintenance PEG-IFN-α-2b or no therapy. Endpoints were similar to the HALT-C trial.

4. Other Strategies: Amelioration of Adverse Host Factors

Given the contribution of host factors such as insulin resistance or hepatic steatosis to diminished PEG-IFN and RBV response rates, another potential avenue might be the amelioration of IR prior to initiation of antiviral therapy in persons with prior nonresponse. In this regard, a number of small pilot studies are being conducted in PEG-IFN and RBV nonresponders to determine whether a course of insulin sensitizing therapy with the thiazolidinediones rosiglitazone or pioglitazone can improve subsequent response to retreatment with PEG-IFN and RBV.

5. Newer Therapies (STAT-C agents) – the future

It is unclear how a pegylated interferon alfa and ribavirin nonresponder patient would fare in clinical trials of single STAT-C agent in combination with peginterferon alfa and ribavirin. One prediction is that a host block in steps downstream from interferon induction (as might be seen in insulin resistance) will persist, and that the result will be the functional equivalent of STAT-C monotherapy. This scenario has been observed in trials of newer antiretroviral agents for HIV added to failing regimens. If that prediction were to be true, then early selection of resistance could be expected, since the magnitude of viral suppression with a single STAT-C agent might not be profound enough to prevent the emergence of resistant variants, and STAT-C agents thus far given as monotherapy are highly associated with selection of resistant variants. In that case, at least two STAT-C compounds, or a STAT-C and a host cofactor inhibitor, would likely be required to improve the magnitude of viral suppression in this population.

However, another possibility is that the administration of a STAT-C agent, such as an NS3/4A protease inhibitor or NS5B polymerase inhibitor, could sensitize the patient to the actions of interferon, and a resurgent peginterferon/ribavirin response would act in concert with the STAT-C agent to produce responses more closely approximating that seen in treatment-naïve patients. These competing hypotheses await clinical trials of peginterferon alfa and ribavirin with STAT-C agents.
Summary

The growing number of patients being treated for chronic HCV has in turn created growing numbers of treatment nonresponders and relapers, for whom treatment options are currently limited. Kinetic considerations suggest that relapers should be offered retreatment with longer duration of therapy to maximize the period of viral undetectability. For those who did not receive optimal doses of RBV during prior treatment, efforts to optimize RBV dose are also in order. For PEG-IFN and RBV nonresponders, there thus far appears to be only modest benefit observed with retreatment using alternative IFNs or higher dose PEG-IFN. Maintenance therapy is being evaluated in several large trials. The decision to pursue maintenance approach should be individualized as we await final data from these trials. The promise of direct antiviral therapy has particular relevance for the nonresponder population, and studies of additive therapy to PEG-IFN and RBV backbones are eagerly awaited, although there remain theoretical concerns in this population.

References