discontinuation for any reason were less frequent in patients treated with PEG IFN-α2a than standard-dose PEG IFN-α2b. In contrast, neutropenia and rash were more frequent in patients treated with PEG IFN-α2a than standard-dose PEG IFN-α2b. In two subsequent head-to-head trials and a systematic review of randomized trials, PEG IFN-α2a was more effective than PEG IFN-α2b (SVR in genotypes 1–4: 48–55% versus 32–40%, respectively). In trials of PEG IFN-α2b among patients with HCV genotype 1, a broader range of weight-based daily ribavirin doses has been validated: 800 mg for weight <65 kg, 1000 mg for weight 65–85 kg, 1200 mg for weight >85–105 kg, and 1400 mg for weight >105 kg. Recommended doses for the two PEG IFNs plus ribavirin and other comparisons between the two therapies are shown in Table 362-6.

Until the 2011 introduction of protease inhibitors, unless ribavirin was contraindicated (see above), combination PEG IFN plus ribavirin was the recommended course of therapy—24 weeks for genotypes 2 and 3 and 48 weeks for genotype 1. For patients with genotypes 1 and 4, the standard of care now includes protease inhibitors or other direct-acting antiviral agents (see below); however, PEG IFN–ribavirin remained the standard of care for patients with genotypes 2 and 3 until late 2013. For patients treated with combination PEG IFN–ribavirin, measurement of quantitative HCV RNA levels at 12 weeks is helpful in guiding therapy; if a 2-$\log_{10}$ drop in HCV RNA has not been achieved by this time, chances for an SVR are negligible, and additional therapy is futile. If the 12-week HCV RNA has fallen by 2 $\log_{10}$ (EVR), the chances for an SVR at the end of therapy are approximately two-thirds; if the 12-week HCV RNA is undetectable ("complete" EVR), the chances for an SVR exceed 80% (Fig. 362-2). Because absence of an EVR is such a strong predictor of the absence of an ultimate SVR, therapy is discontinued for failure to achieve a 12-week 2-$\log_{10}$ drop in HCV RNA (EVR).

Studies have suggested that the frequency of an SVR to PEG IFN–ribavirin therapy can be increased in patients with baseline variables weighing against a response (e.g., HCV RNA $>8 \times 10^5$ IU/mL, weight >85 kg) by raising the dose of PEG IFN (e.g., to as high as 270 μg of PEG IFN-α2a) and/or the dose of ribavirin to as high as 1600 mg daily (if tolerated or supplemented by erythropoietin) or by tailoring treatment based on viral response to prolong the duration of viral clearance before discontinuing therapy, i.e., extending therapy from 48 to 72 weeks for patients with genotype 1 and a slow virologic response (i.e., those whose HCV RNA has not fallen rapidly to undetectable levels within 4 weeks [absence of RVR]). Tailoring therapy based on the kinetics of HCV RNA reduction has also been applied to abbreviating the duration of therapy in patients with genotype 1 (and 4). The results of several clinical trials suggest that, in patients with genotype 1 (and 4) who have a 4-week RVR (which occurs in ≤20%), especially in the subset with low baseline HCV RNA, 24 weeks of therapy with PEG IFN and weight-based ribavirin suffices, yielding SVR rates of ~90% and comparable to those achieved in this cohort with 48 weeks of therapy. Although initial reports suggested that, for patients with genotype 2 and (somewhat less so) genotype 3, in rapid virologic responders with undetectable HCV RNA at week 4, the total duration of therapy required to achieve an SVR could be as short as 12–16 weeks, a very sizable, definitive subsequent trial showed that relapse is increased if treatment duration is curtailed and that a full 24 weeks is superior for these genotypes (except for the minority with very low baseline levels of HCV RNA).

Persons with chronic HCV infection have been shown to suffer increased liver-related mortality. On the other hand, successful antiviral therapy of chronic hepatitis C resulting in an SVR has been shown to improve survival (and to reduce the need for liver transplantation), to lower the risk of liver failure and liver-related death and all-cause deaths, to slow the progression of chronic hepatitis C, and to reverse fibrosis and even cirrhosis. Although successful treatment reduces mortality in cirrhotic patients (and those with advanced fibrosis) and reduces the likelihood of HCC, the risk of liver-related death and HCC persists, albeit at a much reduced level, necessitating continued clinical monitoring and cancer surveillance after SVR in cirrhotics. On the other hand, in the absence of an SVR, routine-dose/duration IFN-based therapy does not reduce the risk of HCC. Similarly, for nonresponders to PEG IFN–ribavirin therapy, three trials of long-term maintenance therapy with PEG IFN have shown no benefit in reducing the risk of histologic progression or clinical decompensation, including the development of HCC. For PEG IFN–ribavirin nonresponders who have had a full, adequate course of therapy, the benefit of retreatment—with higher doses or a longer course of the original PEG IFN regimen or the alternative PEG IFN regimen or with a different type of IFN preparation (e.g., consensus IFN)—is marginal at best. Fortunately, such nonresponders can now be retreated with protease inhibitor-based therapy (see following).

FIRST-GENERATION PROTEASE INHIBITORS (2011–2013)

The HCV RNA genome encodes a single polyprotein, which is cleaved during and after translation by host and viral-encoded proteases. One protease involved in the cleavage of the viral polyprotein is an NS3-4A viral protein that has serine protease activity. Telaprevir and boceprevir are serine protease inhibitors that target NS3-4A. In 2011, telaprevir and boceprevir used in combination with PEG IFN and ribavirin were approved by the U.S. Food and Drug Administration (FDA) for the treatment of hepatitis C genotype 1 in adults with stable liver disease, both in patients who have not been treated before or who have failed previous treatment. Because the presently available HCV protease inhibitors have not been studied comprehensively in patients with genotypes other than 1, their use in these populations is not recommended.

Because resistance develops rapidly, both telaprevir and boceprevir must be used in combination with a PEG IFN and ribavirin-based regimen and should never be used alone. Ribavirin in particular appears to reduce relapse rates significantly in protease inhibitor–based regimens, such that those who cannot take or are intolerant to ribavirin are unlikely to benefit from the addition of these agents. All current telaprevir and boceprevir regimens consist of periods of triple therapy (protease inhibitor plus PEG IFN plus ribavirin) and periods of dual therapy (PEG IFN plus ribavirin). Telaprevir regimens begin with 12 weeks of triple therapy followed by dual therapy of a duration based on HCV RNA status at weeks 4 and 12 ("response-guided therapy") and prior treatment status. Boceprevir-based regimens consist of a 4-week lead-in period of dual (PEG IFN–ribavirin) therapy followed by triple therapy and, in some instances, a further extension of dual therapy, with duration of response-guided therapy based on HCV RNA status at weeks 4, 8, and 24 and prior treatment status **(Table 362-7)**.

For patients with HCV genotype 1, protease inhibitors have significantly improved the frequency of RVRs and SVRs as compared to PEG IFN plus ribavirin alone. In treatment-naïve patients treated with telaprevir, an SVR was seen in up to 79% of patients who received 12 weeks of triple therapy followed by 12–36 weeks of dual therapy, and among those with EVRs (undetectable HCV RNA at weeks 4 and 12) and response-guided therapy stopped at week 24 (12 weeks of triple therapy, then 12 weeks of dual therapy), the rate of SVRs was 83–89% (92% in a subsequent study). In studies with boceprevir in treatment-naïve patients, SVRs were seen in 59–66% of patients, and among those with undetectable HCV RNA at 8 weeks, the SVR rate increased to 86–88%.

Protease inhibitors have also been studied in patients previously treated unsuccessfully with PEG IFN plus ribavirin. In studies with telaprevir, SVRs were seen in 83–88% of patients who had a previous relapse, 54–59% of partial responders (HCV RNA reduced by ≥2 $\log_{10}$ IU/mL but not to undetectable levels), and 29–33% of null responders (HCV RNA reduced by <2 $\log_{10}$ IU/mL). With boceprevir, SVRs occurred in 75% of prior relapsers and in 40–52% of previous partial responders; response rates in null responders are similar to those achieved with telaprevir-based therapy. In a substantial proportion of protease inhibitor nonresponders, resistance-associated variants can be identified, but these variants are not archived, and wild-type HCV reemerges in almost all cases within 1.5 to 2 years. SVRs to these protease inhibitors are highest in prior relapsers and