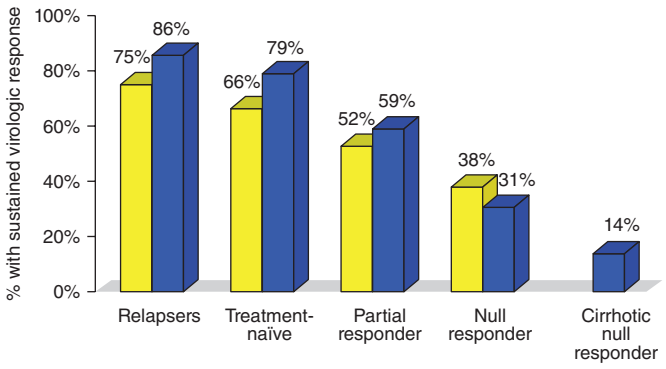

FIGURE 362-3 Maximal efficacy (sustained virologic responses, SVR) of telaprevir (*blue bars*) and boceprevir (*yellow bars*) reported in phase III clinical trials. *(Figure created using data from Bacon BR et al: N Engl J Med 364:1207, 2011; Jacobson IM et al: N Engl J Med 364:2405, 2011; Poordad F et al: N Engl J Med 364:1195, 2011; Zeuzem S et al: N Engl J Med 364:2417, 2011; Vierling JM et al: Hepatology 54 [Suppl 1]:796A-797A, 2011; Ghany MG et al: Hepatology 54:1433, 2011.)*

occasionally requiring transfusion. Complete blood counts should be obtained at baseline and then at 2, 4, 8, and 12 weeks after starting telaprevir. Anemia can occur in half of boceprevir-treated patients, as can neutropenia in up to 30% and thrombocytopenia in 3–4%. Complete blood counts should be obtained at baseline and then at 4, 8, and 12 weeks after starting boceprevir. Other side effects of boceprevir include fatigue, nausea, headache, dysgeusia (altered or unpleasant taste), dry mouth, vomiting, and diarrhea.

Use of protease inhibitors is further complicated by numerous drug-drug interactions. As telaprevir and boceprevir are both eliminated by and inhibit CYP3A4, these agents should not be administered with other medications that induce CYP3A4 or are dependent on CYP3A4 for elimination. Care should be taken to examine for any potential interactions between protease inhibitors and other medications the patient may be taking, because serious adverse events can occur. A convenient website is available to check for such drug-drug interactions (*www.hep-druginteractions.org*).

TREATMENT RECOMMENDATIONS*

Prior to therapy, HCV genotype should be determined, because the genotype dictates the duration of therapy and potentially the agents to be used. PEG IFN plus ribavirin represents the foundation of treatment for all HCV genotypes; patients infected with genotype 1 should also receive a protease inhibitor (telaprevir or boceprevir) when these are available and not contraindicated (Table 362-7). For chronic HCV genotype 1 infection, the AASLD and EASL published treatment guidelines in 2011 reflecting FDA-approved indications for the new protease inhibitors, and in 2012, United Kingdom and French consensus guidelines were published. For treatment-naïve patients and prior relapsers, response-guided therapy with telaprevir or boceprevir is recommended. For telaprevir, the regimen consists of 12 weeks of triple therapy, followed by 12 or 36 weeks of PEG IFN–ribavirin consolidation, depending on whether extended RVR milestones (HCV RNA undetectable at weeks 4 and 12) are met. For boceprevir, the regimen consists of a 4-week PEG IFN–ribavirin lead-in period, followed by 24–32 weeks of triple-drug therapy, depending on whether HCV RNA milestones (undetectable at weeks 8 and 24) are met; if HCV RNA is detectable at week 8 but undetectable at week 24, after 36 weeks of therapy (4-week PEG IFN–ribavirin lead-in plus 32 weeks of triple-drug therapy), an additional 12 weeks of PEG IFN–ribavirin consolidation is recommended. For prior partial and null responders, a full 48-week course of telaprevir (no lead-in period, no response-guided therapy) is recommended; for boceprevir, a 4-week PEG IFN–ribavirin lead-in period is followed by response-guided therapy (32 weeks of triple-drug therapy if HCV RNA is undetectable at weeks 8 and 24 or, if HCV RNA is still detectable at week 8 [but undetectable at week 24], 32 weeks of triple-drug therapy followed by 12 weeks of PEG IFN–ribavirin consolidation). For cirrhotic patients (and for any boceprevir-treated patient whose HCV RNA does not fall by >1 $\log_{10}$ by week 4), a full 48-week course without response-guided therapy should be considered.

Monitoring of HCV plasma RNA is crucial in assessing response to therapy. The goal of treatment is to eradicate HCV RNA, which is predicted by the absence of HCV RNA by PCR 6 months after stopping treatment (SVR). When therapy relied on PEG IFN and ribavirin, failure to achieve a 2-$\log_{10}$ drop in HCV RNA by week 12 of therapy (EVR) rendered it unlikely that further therapy would result in an SVR. When PEG IFN and ribavirin are part of a protease inhibitor regimen, HCV RNA should be measured at baseline and at weeks 4, 8 (for boceprevir), 12, and 24 to assess response to treatment and to aid in decisions regarding treatment duration (response-guided therapy), as well as 12 and 24 weeks after therapy. Stopping rules are important to prevent the emergence of resistance; if HCV RNA is >1000 IU/mL at 4 or 12 weeks of telaprevir (or still detectable at week 24), or if HCV RNA is ≥100 IU/mL at week 12 of boceprevir (or detectable at week 24), all treatment should be stopped.

INDICATIONS FOR ANTIVIRAL THERAPY*

Patients with chronic hepatitis C who have detectable HCV RNA in serum, whether or not aminotransferase levels are increased, and chronic hepatitis of at least moderate grade and stage (portal or bridging fibrosis) are candidates for antiviral therapy with PEG IFN plus ribavirin. Most authorities recommend 800 mg of ribavirin for patients with genotypes 2 and 3 for both types of PEG IFN and weight-based 1000–1200 mg (when used with PEG IFN-α2a) or 800–1400 mg (when used with PEG IFN-α2b) ribavirin for patients with genotype 1 (and 4), unless ribavirin is contraindicated (Table 362-7). These PEG IFN and ribavirin doses are used with protease inhibitors for patients with genotype 1 (Table 362-7). Although patients with persistently normal ALT activity tend to progress histologically very slowly or not at all, they respond to antiviral therapy just as well as do patients with elevated ALT levels; therefore, although observation without therapy is an option, such patients are potential candidates for antiviral therapy. As noted above, therapy with IFN has been shown to improve survival and complication-free survival and to slow progression of (and to reverse) fibrosis.

HCV genotype determines the duration of PEG IFN and ribavirin therapy: 24 weeks for those with genotypes 2 and 3 and 48 weeks for patients with genotypes 4 and 1 (in patients for whom protease inhibitors are not available or contraindicated). For patients with genotype 4, treatment should be discontinued in patients who do not achieve an EVR at week 12. For patients with genotypes 2 and 3, a full, 24-week course is most effective, although the duration may be reduced to 12–16 weeks for patients with genotype 2, a low baseline level of viremia, and an RVR, especially to be considered for patients who tolerate therapy poorly. Also, consideration should be given to increasing the duration of therapy to 48 weeks for patients with genotype 3 who have advanced fibrosis and/or a high baseline level of viremia. As noted above, the absence of a 2-$\log_{10}$ drop in HCV RNA at week 12 (EVR) weighs heavily against the likelihood of an SVR; therefore, measuring HCV RNA at 12 weeks is recommended routinely (Fig. 362-2), and therapy can be discontinued if an EVR is not achieved. Among patients with genotype 4 who achieve an

*As this chapter was going to press, two additional antiviral drugs, a second-generation protease inhibitor simeprevir and nucleoside analogue polymerase inhibitor sofosbuvir were approved for the treatment of hepatitis C. Simerprevir, which is effective for genotype 1, must be administered, like first-generation protease inhibitors, for 12 weeks with PEG IFN and ribavirin, followed by another 12 weeks of PEG IFN and ribavirin (no response-guided therapy). Sofosbuvir, the more convenient and broadly applicable of the two new drugs, must be administered with PEG IFN and ribavirin but for only 12 weeks in patients with genotyes 1, 4-6; for patients with genotypes 2 and 3, PEG IFN is not required. Sofosbuvir plus ribavirin are administered for 12 weeks in genotype 2 and for 24 weeks in genotype 3. Antiviral therapy is evolving very rapidly; by the end of 2014, all-oral, interferon-free combinations (e.g., sofosbuvir plus the NS5a inhibitor ledipasvir) will supplant earlier treatment regimens. For updated treatment recommendations, please consult *www.hcvguidelines.org.*