ribavirin dose reductions or addition of erythropoietin to boost red blood cell levels may be required; erythropoietin has been shown to improve patients' quality of life but not the likelihood of achieving an SVR. If ribavirin is stopped during therapy, SVR rates fall, but responsiveness can be maintained as long as ribavirin is not stopped and the total ribavirin dose exceeds 60% of the planned dose. In addition, ribavirin, which is excreted renally, should not be used in patients with renal insufficiency; the drug is teratogenic, precluding its use during pregnancy and mandating the scrupulous use of efficient contraception during therapy (IFNs, too, because of their antiproliferative properties, are contraindicated during pregnancy).

Ribavirin can also cause nasal and chest congestion, pruritus, and precipitation of gout. Combination IFN-ribavirin therapy is more difficult to tolerate than IFN monotherapy. In one large clinical trial of combination therapy versus monotherapy, among those in the 1-year treatment group, 21% of the combination group (but only 14% of the monotherapy group) had to discontinue treatment, whereas 26% of the combination group (but only 9% of the monotherapy group) required dose reductions.

Studies of viral kinetics have shown that despite a virion half-life in serum of only 2–3 h, the level of HCV is maintained by a high replication rate of 10^{12} hepatitis C virions per day. IFN-α blocks virion production or release with an efficacy that increases with increasing drug doses; moreover, the calculated death rate for infected cells during IFN therapy is inversely related to level of HCV RNA; patients with the most rapid death rate of infected hepatocytes are more likely to achieve undetectable HCV RNA at 3 months; in practice, failure to achieve an early virologic response (EVR), a ≥2-$\log_{10}$ reduction in HCV RNA by week 12, predicts failure to experience a subsequent SVR. Similarly, patients in whom HCV RNA becomes undetectable within 4 weeks (i.e., who achieve a rapid virologic response [RVR]) have a very high likelihood of achieving an SVR (Fig. 362-2). Therefore, to achieve rapid viral clearance from serum and the liver, *high-dose induction therapy* has been advocated. In practice, however, high-dose induction with IFN-based therapy has not yielded higher sustained response rates.

For the treatment of chronic hepatitis C, standard IFNs were supplanted by PEG IFNs. These have elimination times up to sevenfold longer than standard IFNs (i.e., a substantially longer half-life) and achieve prolonged concentrations, permitting administration once (rather than three times) a week. Instead of the frequent drug peaks (linked to side effects) and troughs (when drug is absent) associated with frequent administration of short-acting IFNs, administration of PEG IFNs results in drug concentrations that are more stable and sustained over time. Once-a-week PEG IFN monotherapy is twice as effective as monotherapy with its standard IFN counterpart, approaches the efficacy of combination standard IFN plus ribavirin, and is as well tolerated as standard IFNs, without more difficult-to-manage thrombocytopenia and leukopenia than standard IFNs. For most of the decade prior to 2011, when protease inhibitors were introduced for HCV genotype 1 (see below), the standard of care was a combination of PEG IFN plus ribavirin for all HCV genotypes.

Two PEG IFNs are available: PEG IFN-α2b and -α2a. PEG IFN-α2b consists of a 12-kD, linear PEG molecule bound to IFN-α2b, whereas PEG IFN-α2a consists of a larger, 40-kD, branched PEG molecule bound to IFN-α2a; because of its larger size and smaller volume of extravascular distribution, PEG IFN-α2a can be given at a uniform dose independent of weight, whereas the dose of the smaller PEG IFN-α2b, which has a much wider volume distribution, must be weight-based **(Table 362-6)**. In the registration trial for PEG IFN-α2b plus ribavirin, the best regimen was 48 weeks of 1.5 μg/kg of PEG IFN once a week plus 800 mg of ribavirin daily. A post hoc analysis suggested that weight-based dosing of ribavirin would have been more effective than the fixed 800-mg dose used in the study (a broader dose/weight range was approved subsequently; see below). In the first registration trial for PEG IFN-α2a plus ribavirin, the best regimen was 48 weeks of 180 μg of PEG IFN plus 1000 mg (for patients <75 kg) to 1200 mg (for patients ≥75 kg) of ribavirin. SVRs of 54 and 56% were reported in these two studies, respectively. A subsequent study of PEG IFN-α2a plus ribavirin showed that, for patients with genotypes 2 and 3, a duration of 24 weeks and a ribavirin dose of 800 mg were sufficient. Among the three studies, for patients in the optimal treatment arm, SVR rates for patients with genotype 1 were 42–51%, and for patients with genotypes 2 and 3, rates were 76–82%. Between genotypes 2 and 3, genotype 3 is somewhat more refractory, and some authorities would extend therapy for a full 48 weeks in patients with genotype 3, especially if they have advanced hepatic fibrosis or cirrhosis and/or high-level HCV RNA.

In the initial registration trials for combination PEG IFN plus ribavirin, both combination PEG IFN regimens were compared to standard IFN-α2b plus ribavirin. Side effects of the combination PEG IFN-α2b regimen were comparable to those for the combination standard IFN regimen; however, when the combination PEG IFN-α2a regimen was compared with the combination standard IFN-α2b regimen, flu-like symptoms and depression were less common in the combination PEG IFN group. Although ascertainment of side effects differed between studies of the two drugs, when each was tested against standard IFN-α2b plus ribavirin, combination PEG IFN-α2a plus ribavirin appeared to be better tolerated. In a head-to-head trial of the two PEG IFNs (the IDEAL trial), the two PEG IFNs were found to be comparable in efficacy (achievement of SVR) and tolerability, although headache, nausea, fever, myalgia, depression, and drug

TABLE 362-6 PEGYLATED INTERFERON (PEG IFN) α2a AND α2b FOR CHRONIC HEPATITIS C

	PEG IFN-α2b	PEG IFN-α2a
PEG size	12 kD linear	40 kD branched
Elimination half-life	54 h	65 h
Clearance	725 mL/h	60 mL/h
Dose	1.5 μg/kg (weight-based)	180 μg
Storage	Room temperature	Refrigerated
Ribavirin dose		
Genotype 1	800–1400 mg[a]	1000–1200 mg[b]
Genotype 2/3	800 mg	800 mg
Duration of therapy		
Genotype 1	48 weeks	48 weeks
Genotype 2/3	48 weeks[c]	24 weeks
Efficacy of combination therapy[d]	54%	56%
Genotype 1	40–42%	41–51%
Genotype 2/3	82%	76–78%

[a]In the registration trial for PEG IFN-α2b plus ribavirin, the optimal regimen was 1.5 μg of PEG IFN plus 800 mg of ribavirin; however, a post hoc analysis of this study suggested that higher ribavirin doses are better. In subsequent trials of PEG IFN-α2b with ribavirin in patients with genotype 1, the following daily ribavirin doses have been validated: 800 mg for patients weighing <65 kg, 1000 mg for patients weighing >65–85 kg, 1200 for patients weighing >85–105 kg, and 1400 mg for patients weighing >105 kg. [b]1000 mg for patients weighing <75 kg; 1200 mg for patients weighing ≥75 kg. [c]In the registration trial for PEG IFN-α2b plus ribavirin, all patients were treated for 48 weeks; however, data from other trials of standard interferons and the other PEG IFN demonstrated that 24 weeks suffices for patients with genotypes 2 and 3. For patients with genotype 3 who have advanced fibrosis/cirrhosis and/or high-level HCV RNA, a full 48 weeks is preferable. [d]Attempts to compare the two PEG IFN preparations based on the results of registration clinical trials are confounded by differences between trials of the two agents in methodologic details (different ribavirin doses, different methods for recording depression, and other side effects) and study-population composition (different proportion with bridging fibrosis/cirrhosis, proportion from the United States versus international, mean weight, proportion with genotype 1, and proportion with high-level HCV RNA). In the head-to-head comparison of the two PEG IFN preparations in the IDEAL trial reported in 2009, the two drugs were comparable in tolerability and efficacy. PEG IFN-α2b was administered at a weekly weight-based dose of 1.0 μg/kg or 1.5 μg/kg, and PEG IFN-α2a at a weekly fixed dose of 180 μg. For PEG IFN-α2b, daily ribavirin weight-based doses ranged between 800 and 1400 mg based on weight criteria (see footnote *a*, above), whereas for PEG IFN-α2a, daily ribavirin weight-based doses ranged between 1000 and 1200 mg (see footnote *b*, above). For the two PEG IFN-α2b study arms, ribavirin dose reductions for ribavirin-associated adverse effects were done in 200- to 400-mg decrements; for PEG IFN-α2a, the ribavirin dose was reduced to 600 mg for intolerability. Sustained virologic responses occurred in 38.0% of the low-dose PEG IFN-α2b group, 39.8% of the standard, full-dose PEG IFN-α2b group, and 40.9% of the PEG IFN-α2a group.

Abbreviations: HCV RNA, hepatitis C virus RNA; PEG, polyethylene glycol.