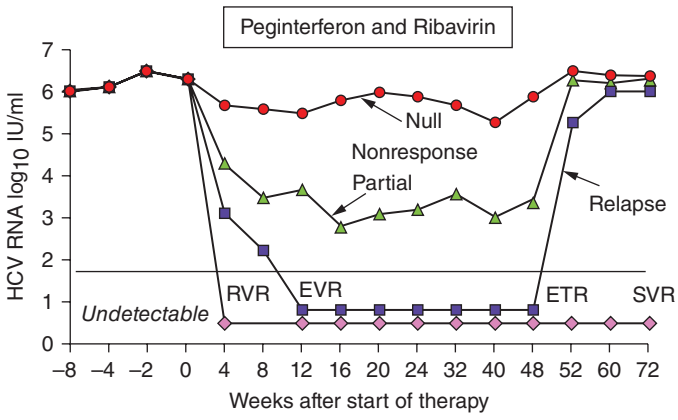

FIGURE 362-2 Classification of virologic responses based on outcomes during and after a 48-week course of pegylated interferon (PEG IFN) plus ribavirin antiviral therapy in patients with hepatitis C, genotype 1 or 4 (for genotype 2 or 3, the course would be 24 weeks). Nonresponders can be classified as null responders (hepatitis C virus [HCV] RNA reduction of <2 $\log_{10}$ IU/mL) or partial responders (HCV RNA reduction ≥2 $\log_{10}$ IU/mL but not suppressed to undetectable) by week 24 of therapy. In responders, HCV RNA can become undetectable, as shown with sensitive amplification assays, within 4 weeks (RVR, rapid virologic response); can be reduced by ≥2 $\log_{10}$ IU/mL within 12 weeks (early virologic response, EVR; if HCV RNA is undetectable at 12 weeks, the designation is "complete" EVR); or at the end of therapy, 48 weeks (ETR, end-treatment response). In responders, if HCV RNA remains undetectable for 24 weeks after ETR, week 72, the patient has a sustained virologic response (SVR), but if HCV RNA becomes detectable again, the patient is considered to have relapsed. In patients treated with protease inhibitor–based therapy, several additional milestones are monitored: (1) among boceprevir-treated patients, the level of HCV RNA reduction (>1 $\log_{10}$ or ≥1 $\log_{10}$ IU/mL) during the 4-week PEG IFN–ribavirin lead-in phase; (2) during boceprevir therapy, undetectable HCV RNA at week 8 (week 4 of triple-drug therapy; RVR); and (3) among telaprevir-treated patients, undetectable HCV RNA at week 4 and 12 (extended RVR). *(Reproduced with permission, courtesy of Marc G. Ghany, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health and the American Association for the Study of Liver Diseases. Hepatology 49:1335, 2009.)*

of guanosine pools), immune modulation, induction of virologic mutational catastrophe, and enhancement of IFN-stimulated gene expression. IFN therapy results in activation of the JAK-STAT signal transduction pathway, which culminates in the intracellular elaboration of genes and their protein products that have antiviral properties. Hepatitis C proteins inhibit JAK-STAT signaling at several steps along the pathway, and exogenous IFN restores expression of IFN-stimulated genes and their antiviral effects.

Treatment with the combination of PEG IFN and ribavirin increased responsiveness (frequency of SVR) to as high as 55% overall, to >40% in genotypes 1 and 4, and to >80% in genotypes 2 and 3. Still, many important lessons about antiviral therapy for chronic hepatitis C were learned from the experience with IFN monotherapy and combination IFN-ribavirin therapy. Even in the absence of biochemical and virologic responses, histologic improvement occurs in approximately three-fourths of all treated patients. In chronic hepatitis C, unlike the case in hepatitis B, responses to therapy are not accompanied by transient, acute hepatitis-like aminotransferase elevations. Instead, ALT levels fall precipitously during therapy. Up to 90% of virologic responses are achieved within the first 12 weeks of therapy; responses thereafter are rare. Most relapses occur within the first 12 weeks after treatment; therefore, an SVR at week 12 posttreatment is roughly equivalent to a 24-week SVR. SVRs are very durable; normal ALT, improved histology, and absence of HCV RNA in serum and liver have been documented a decade after successful therapy, and "relapses" 2 years after sustained responses are almost unheard of. Thus, an SVR to antiviral therapy of chronic hepatitis C is tantamount to a cure.

Patient variables that tend to correlate with sustained virologic responsiveness to IFN-based therapy include favorable genotype (genotypes 2 and 3 as opposed to genotypes 1 and 4); low baseline HCV RNA level (<2 million copies/mL, which is equivalent to <800,000 IU/mL, the current convention of quantitation); histologically mild hepatitis and minimal fibrosis; age <40; female gender; and absence of obesity, insulin resistance, and type 2 diabetes mellitus. Patients with cirrhosis can respond, but they are less likely to do so. For patients treated with combination IFN-ribavirin, therapy for those with genotype 1 should last a full 48 weeks, whereas in those with genotypes 2 and 3, a 24-week course of therapy suffices (although refined tailoring of treatment duration may be indicated based on rapidity of response or associated cofactors, see below). The response rate in African Americans is disappointingly low for reasons that are not fully understood. Potentially contributing to, but not explaining entirely, low responsiveness in African Americans are a higher proportion with genotype 1, slower early viral kinetics during therapy, impaired HCV-specific immunity, and recently recognized host genetic differences in *IL28B* alleles, described below. The response rate in Latino patients is also low, despite the fact that the frequency of the favorable *IL28B* C allele is as common in Hispanic patients as in whites. Moreover, the likelihood of a sustained response is best if adherence to the treatment regimen is high (i.e., if patients receive ≥80% of the IFN and ribavirin doses and if they continue treatment for ≥80% of the anticipated duration of therapy). Other variables reported to correlate with increased responsiveness include brief duration of infection, low HCV quasispecies diversity, immunocompetence, absence of hepatic steatosis, and low liver iron levels. High levels of HCV RNA, more histologically advanced liver disease, and high quasispecies diversity all go hand in hand with advanced duration of infection, which is one of the most important clinical variables determining IFN responsiveness. The ironic fact, then, is that patients whose disease is least likely to progress are the ones *most* likely to respond to IFN and vice versa.

Genetic changes in the virus may explain differences in treatment responsiveness in some patients (e.g., among patients with genotype 1b, responsiveness to IFN is enhanced in those with amino-acid-substitution mutations in the nonstructural protein 5A gene). As described above in the discussion of spontaneous recovery from acute hepatitis C, IFN gene variants discovered recently in genome-wide association studies have been shown to have a substantial impact on responsiveness of patients with genotype 1 to antiviral therapy. In studies of patients treated with PEG IFN and ribavirin, variants of the *IL28B* SNP that code for IFN-λ3 (a type III IFN, the receptors for which are more discretely distributed than IFN-α receptors and more concentrated in hepatocytes) correlate significantly with responsiveness. Patients homozygous for the C allele at this locus have the highest frequency of achieving an SVR (~80%), those homozygous for the T allele at this locus are least likely to achieve an SVR (~25%), and those heterozygous at this locus (C/T) have an intermediate level of responsiveness (SVRs in ~35%). The fact that C/C is common in whites of European ancestry and even more so in Japanese persons but rare in African Americans helps explain the differences in observed responsiveness among these population groups.

Side effects of IFN therapy are described above in the section on treatment of chronic hepatitis B. The most pronounced side effect of ribavirin therapy is hemolysis; a reduction in hemoglobin of up to 2–3 g or in hematocrit of 5–10% can be anticipated. A small, unpredictable proportion of patients experience profound, brisk hemolysis, resulting in symptomatic anemia; therefore, close monitoring of blood counts is crucial, and ribavirin should be avoided in patients with anemia or hemoglobinopathies and in patients with coronary artery disease or cerebrovascular disease, in whom anemia can precipitate an ischemic event. When symptomatic anemia occurs,