To ensure that the characteristics of subjects in each of the three study arms were similar, subjects were stratified as follows:

- *First stratum*. Plasma levels of HCV-RNA (less than or equal to 600,000 IU/mL vs greater than 600,000 IU/mL) and
- *Second stratum*. Race (African-American vs non-African-American).

The results were as follows. The values for SVR were about the same for all three arms, that is, about 40%. In the words of the authors, "the rates of sustained virologic response were similar among the three groups."

The values for relapse rate were more favorable to the patients receiving IFN-alpha-2b (about 22% relapse rate), and less favorable for patients receiving IFN-alpha-2a (31.5% relapse rate). According to the authors, "patients treated with peginterferon-alfa-2a were more likely to have a response while receiving therapy, followed by relapse after the completion of therapy."

b. Endpoints of the Di Bisceglie Study

The clinical trial of chronic HCV by Di Bisceglie et al. (80) had two study arms, as indicated:

- *Arm A*. Pegylated IFN-alpha-2a.
- *Arm B*. Placebo (no drugs).

All of the subjects had chronic hepatitis C and advanced fibrosis. All of the subjects had been previously treated with pegylated interferon and ribavirin, but had not responded. As mentioned earlier in this chapter, it is the case that SVR occurs in only half of patients treated with the standard of care. Subjects were stratified in order to ensure that the characteristics of subjects allocated to Arm A and Arm B were similar. Stratification was according to stage of liver fibrosis (noncirrhotic fibrosis vs cirrhotic fibrosis).

Regarding ethics, it should be noted that where potential study subjects had earlier failed to respond to treatment by the standard of care, administering placebo in a subsequent clinical trial is ethical. According to Daugherty et al. (81) and Amdur and Biddle (82), placebo controls are increasingly being used when the standard of care is ineffective.

The Di Bisceglie study addressed the possibility that long-term "maintenance" therapy with interferon might be effective in controlling the disease.

The primary endpoint was progression of liver disease. Progression of liver disease encompasses all of these events:

- death,
- hepatocellular carcinoma,
- hepatic decompensation, for example, variceal hemorrhage,
- increase in fibrosis score, as determined with liver biopsies.

The secondary endpoints were:

- serum aminotransferase,
- serum HCV-RNA,
- histologic necroinflammatory scores (determined with liver biopsies at baseline, at 1.5 years, and 3.5 years).

The study drug did not improve the primary endpoint. The response rate, as

[80]Di Bisceglie AM, Shiffman ML, Everson GT, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. New Engl. J. Med. 2008;359:2429–41.

[81]Daugherty CK, Ratain MJ, Emanuel EJ, Farrell AT, Schilsky RL. Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials. J. Clin. Oncol. 2008;26:1371–8.

[82]Amdur RJ, Biddle CJ. An algorithm for evaluating the ethics of a placebo-controlled trial. Int. J. Cancer 2001;96:261–9.