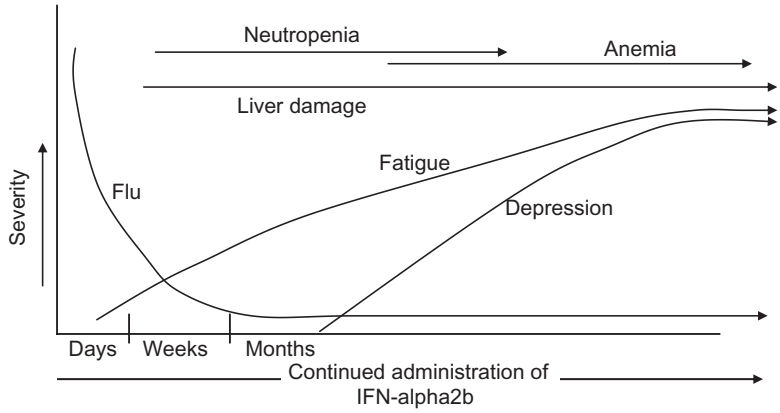

Figure 24.1 Adverse events occurring with administration of interferon-alpha2b. The adverse events include hematological parameters, that is, neutrophil counts and red blood cell counts, as well as patient-reported outcomes, fatigue and depression

is called *tachyphylaxis*. The flu-like symptoms are fever, chills, headache, myalgia, nausea, and vomiting. Fatigue increases in intensity as therapy continues and it can be very debilitating. Levels of hepatic enzymes, as measured in serum samples, are assayed on a weekly basis in order to monitor drug-induced liver toxicity. Where liver toxicity presents, the physician may respond by lowering the dose, or delaying dosing, of the IFN-alpha2b. In the context of a clinical trial, this response is called *dose modification*.

c. Anticipating adverse events in the design of clinical studies

Planning the study design includes planning which types of adverse events should be monitored. According to the ICH Guidelines (17):

> *[a] hierarchy of organ systems can be developed according to their importance with respect to life-supporting functions. Vital organs or systems, the functions of which are acutely critical for life, such as the cardiovascular, respiratory and central nervous systems, are considered to be the most important ones to assess in safety pharmacology studies. Other organ systems, such as the renal or gastrointestinal system, the functions of which can be transiently disrupted by adverse pharmacodynamic effects without causing irreversible harm, are of less immediate investigative concern.*

The ICH Guidelines specifically focus on adverse events involving the immune system, and where these adverse events reside in two categories, namely, where a study drug impairs the immune system, and where the study drug induces immune system-mediated harm to various tissues of the body (18):

[17] ICH Harmonised Tripartite Guideline. Safety pharmacology studies for human pharmaceuticals S7A. Step 4 version, November 2000, 9 pages.

[18] ICH Harmonised Tripartite Guideline. Immunotoxicity studies for human pharmaceuticals S8. Step 4 version, September 2005, 14 pages.