

12

QUESTION

HOW DO I KNOW WHEN A PATIENT RECEIVING AN ORAL ANTIVIRAL AGENT HAS DEVELOPED RESISTANCE AND WHAT DO I DO WHEN THIS HAPPENS?

Mitchell L. Shiffman, MD

Resistance is the major limitation when utilizing an oral antiviral agent for the treatment of chronic hepatitis B virus (HBV). Although it is commonly believed that resistant mutations develop in response to treatment with antiviral agents, the great majority of mutations that convey resistance to antiviral therapy are actually preexisting.¹ Mutations are single nucleotide substitutions (SNPs) that occur in the viral genome. This changes the nucleic acid sequence of a viral gene. In many cases these SNPs have no effect on the amino acid sequence, structure, or function of the protein produced by this genetic mutation. However, in some cases an SNP may change a critical amino acid within the protein product of a gene, and this may have a wide range of effects, as listed in Table 12-1. Some mutations are lethal and prevent the virus from reproducing itself. Such mutated viral strains cease to exist soon after they are formed. Some mutations alter proteins so that they are no longer produced or recognized by serologic testing. In patients with chronic HBV the most common example of this is an SNP that prevents the production of E-antigen. Other SNPs in the HBV genome cause changes to the amino acid sequence of S-antigen or core protein, which in some cases may prevent these proteins or their antibodies from being recognized by standard serologic tests utilized to assess for HBV infection (see Question 9). Other SNPs may affect the ability of antiviral agents to suppress HBV replication.

SNPs within the viral genome occur randomly at regular intervals. As a result, most viruses, including HBV, exist as a family of genetically similar but distinct viral species, as illustrated in Figure 12-1. In general, the naturally occurring form of the virus dominates and is present in the highest concentration. This is referred to as the wild type of the virus. Mutated forms of the virus are generally present at much lower concentrations.