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Short communication

The implications of drug resistance for strategies of combination antiviral chemotherapy

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The sites and mechanisms of action of both the activity and the resistance to antiviral drugs have been characterized more precisely than have those for any other class of drugs (Richman, 1994a). The next step is the rational translation of our understanding of the pathogenesis of viral diseases and the responses of virus replication to intervention with antiviral drugs in the design of combination regimens for the durable, effective control of viral disease.

Drug treatment selects for the emergence of resistant mutants. For single stranded RNA viruses, whose genomic replication lacks a proofreading mechanism, the mutation frequencies are approximately 10^{-4}. Thus, a single 10-kilobase genome, like that of human immunodeficiency virus (HIV), would be expected to contain on average one mutation in each progeny viral genome. Many virus infections are characterized by high levels of virus replication with high rates of virus turnover. This is especially true of the chronic infection with HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV). For this reason, resistance also occurs more frequently with herpesvirus infections in immunosuppressed patients such as those with transplants and HIV infection. Evidence is increasingly accumulating for the preexistence of drug resistant subpopulations in virus infection (Nájera et al., 1994; Nájera et al., 1995; Havlir et al., 1995b; Kozal et al., 1995). Such mutations are even more prevalent when high levels of virus replication are occurring.

The practical question is to dissect out the component of clinical failure of patients treated with antiviral drugs that is attributable to the acquisition of drug resistance. Ascertaining the contribution of drug resistance to drug failure is a difficult problem because patients who are more likely to develop drug resistance are more likely to have other confounding factors that will predispose to a poor prognosis (Richman, 1994b). Moreover, associations of resistant virus with clinical endpoints is complicated by the fact that patients contain mixtures of viruses with different susceptibilities and these different populations may be represented differently in different organs

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of patients under treatment. For example, is the susceptibility to ganciclovir of cytomegalovirus (CMV) that is causing retinitis reflected by the susceptibility of the more accessible isolates in the blood or urine?

The association of drug resistance with loss of activity of antiviral therapy have been reviewed in the literature in general (Richman, 1994a) with specific reviews with more detail for influenza, (Hayden and Couch, 1992; Monto and Arden, 1992) herpesviruses (Coen, 1991) and HIV (Richman, 1994c; Richman, 1995). The issue is how to design regimens that sustain activity despite the emergence of drug resistance.

Three theoretical mechanisms to sustain antiretroviral drug activity despite the development of drug resistance can be proposed: 1. Plasma levels of drug can be generated that exceed the susceptibility of drug resistant virus. This assumes appropriate pharmacologic characteristics of the drug and constraints on the mutability of the target viral protein. An example of some limited success with this strategy has been presented with the non-nucleoside reverse transcriptase inhibitor of HIV, nevirapine (Havlir et al., 1995a). 2. Drug resistance mutations, which confer a clear selective advantage in the face of drug pressure, may still impair the replicative capacity of the virus compared to that of the wild type virus in the absence of treatment. Such attenuated virus may contribute to the activity of lamivudine and perhaps some protease mutants (Schuurman et al., 1995; Ho et al., 1994). 3. For two drugs targeted to the same viral protein (convergent therapy), mutations induced by drug 1 may sensitize the virus to drug 2 or may prevent the emergence of viable mutants to drug 2 (Chow et al., 1993). The mutation from methionine to valine at residue 184 of reverse transcriptase, which emerges with lamivudine treatment suppresses the critical mutation at residue 215 that confers resistance to AZT (Tisdale et al., 1993). Combinations of protease inhibitors may also exploit this strategy. It seems logical that a potent inhibitor can be designed to the active site of viruses highly resistant to other protease inhibitors (Erickson, 1995).

Strategies to identify effective combination regimens to control virus infections, especially those characterized by chronic high levels of virus replication, must exploit these three approaches to achieve the goal of suppressing virus replication to as great a magnitude as possible for as long as possible. Data, as yet unpublished, are beginning to emerge with HIV infection that resistant mutants are emerging more slowly with regimens of protease inhibitors that produce larger and more sustained reductions of plasma HIV RNA. In Fig. 1, a relationship between increasing antiviral activity and the probability of the emergence of drug resistant mutants is depicted.

With increasing drug exposure, the selective pressure on the replicating virus population increases to promote the more rapid emergence of drug resistant mutants. As antiviral drug activity increases still more, the amount of virus replication diminishes to the point where the likelihood of emergence of resistance begins to diminish. This likelihood becomes nil when virus replication is completely inhibited. Thus, the ultimate goal of the chemotherapy of viral infection — no different from that for the chemotherapy of tuberculosis or malignancy — is to identify drug regimens that completely inhibit virus replication. In the meantime, because symptoms and death with chronic viral infections are correlated with the magnitude of the steady state levels of virus, prolonged partial suppression of virus replication

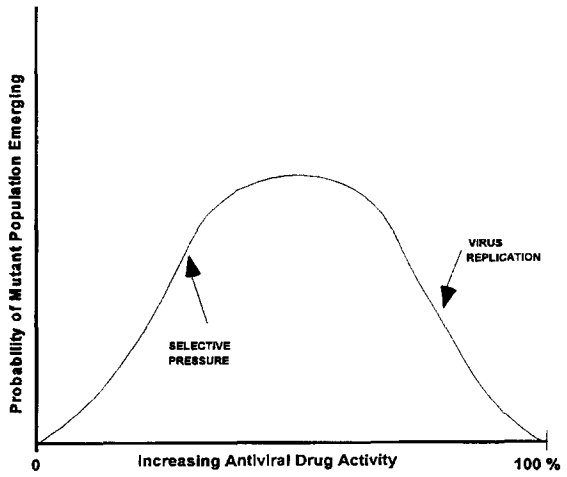

Fig. 1. The relationship between drug activity and the emergence of drug resistant mutants.

represents a reasonable and achievable intermediate goal.

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