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Short communication

Combination therapy in primary HIV infection

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Current guidelines for the initiation of antiviral therapy are based on the occurrence of opportunistic infections and on the CD4+ levels. New concepts of the pathogenesis of HIV infection (Fauci, 1993; Wei et al., 1995) argue in favor of early treatment in asymptomatic patients: HIV replication is a continuous process starting before symptoms arise, chemotherapy is more effective in the early stages of several infectious diseases, therapy is better tolerated, and surrogate markers respond better early in HIV disease.

When considering patients with primary HIV infection (PHI), there are additional arguments in favor of antiviral therapy to be initiated as early as possible. First, most patients identified with PHI present with an acute illness and these symptomatic patients have a worse long-term prognosis (Lindbäck et al., 1994). Second, levels of viremia are very high around seroconversion and allow for widespread dissemination of the virus, for example, into the central nervous system. Third, viral populations are still homogenous at the time of PHI. As viral heterogeneity increases with the number of replication cycles, generation of millions to billions of genetically distinct mutants occur and this, in turn, leads to an increasing concentration of preexistent drug-resistant mutant viruses in latently-infected cells. Upon initiation of antiviral treatment later in the course of the disease, drug resistant mutants will emerge more rapidly.

A tentative goal for antiviral treatment could be to transform the majority of PHI patients into long-term non-progressors (Pantaleo et al., 1995). In this subgroup of patients, viral replication is controlled durably and CD4+ cells remain within the normal range 7–12 years after infection. Also, in contrast to the progressive destruction of lymph nodes in the majority of HIV patients, normal lymph node architecture is retained in these patients.

To assess the efficacy of antiviral treatment in PHI we need: (a) appropriate tools to monitor therapeutic efficacy; new assays are now available for the measurement of viral load and their use in conjunction with immunological markers may be used as substitutes for clinical end points, (b) effective treatments and (c) a long-term strategy in terms of duration and changes in therapy.

Two clinical studies have investigated the effect of zidovudine treatment in PHI patients (Niu et al., 1993; Kinloch-de Loës et al., 1995) and have

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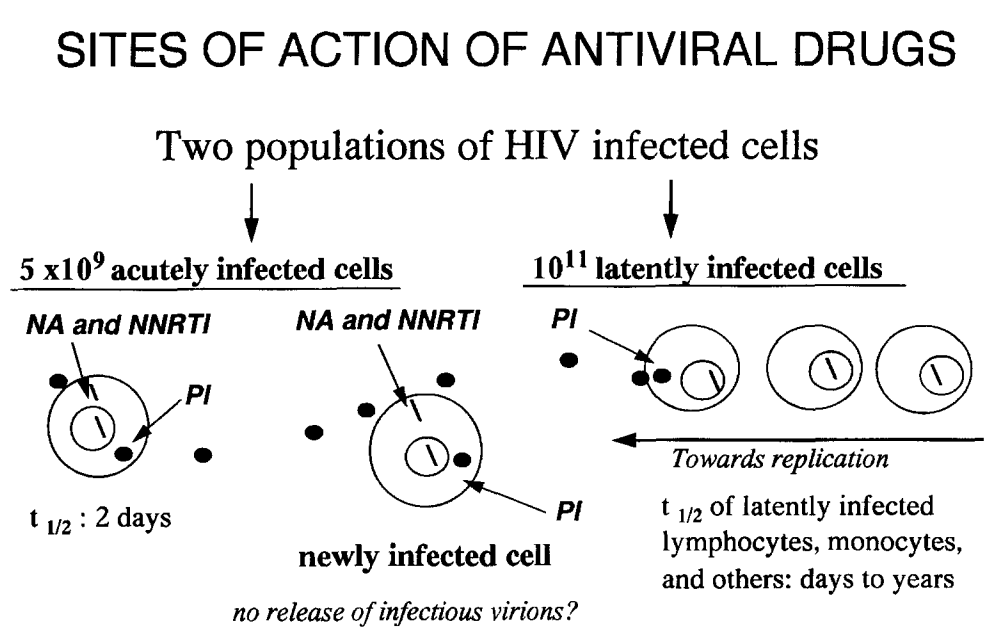

Fig. 1. Sites of action of antiviral drugs acting on HIV reverse transcriptase (NA, nucleoside analogues; NNRTI, non-nucleoside reverse transcriptase inhibitors) and on HIV protease (PI, protease inhibitors). The two main compartments of HIV-infected cells are represented, namely acutely-infected cells actively replicating HIV and the latently-infected cells which contain integrated proviral DNA but do not actively replicate HIV.

shown that zidovudine treatment stabilizes or increases CD4+ cell counts, and is associated with clinical benefit. The impact of zidovudine remains limited when considering viremia levels (non significant decrease). Antiviral therapy for 6 months did not induce reverse transcriptase (RT) mutations associated with zidovudine resistance.

These studies indicate that the tentative goal of controlling viral replication can not be reached with monotherapy. Future intervention strategies should combine two or more drugs and may be pursued along two lines, using either convergent or divergent therapy. In theory, several steps of HIV replication can be the target of antiviral drugs, including cellular binding and penetration of HIV, reverse transcription, integration of provirus into the host genome, translation, virus assembly, etc. Presently, only antiviral drugs interfering with HIV reverse transcriptase and the viral protease are available for clinical trials and we shall therefore focus on these two classes of compounds.

The aim of convergent therapy is to fully inhibit enzyme activity by directing two or more drugs at the same viral target, and thus to prevent viral replication. If this goal is not reached, selection pressures resulting into the simultaneous development of multiple enzyme mutations may still decrease enzymatic activity and slow down viral replication.

The challenge of convergent therapy is to achieve a maximal antiviral effect with minimal toxicity. Recent data on the efficacy of the combination of zidovudine and lamivudine are encouraging and this drug regimen could be one of the therapeutic options available, with or without the addition of a non-nucleoside inhibitor of the reverse transcriptase (NNRTI). The antiviral efficacy of the combination of other nucleoside analogues, including the newly-developed drugs should also be assessed. Combination of antiproteases may display additive effects.

Divergent therapy involves a combination of antiviral agents targeting different sites of viral replication. The main advantage of combining

reverse transcriptase and protease inhibitors is shown in Fig. 1. Only protease inhibitors can reduce the production of infectious virions by latently-infected cells when they enter into replication. Although these cells do not produce the bulk of circulating viruses, they still represent the majority of the pool of HIV-infected cells and contain the whole array of viral genotypes. In addition, viruses which escape the action of protease inhibitor(s) could be later targeted by RT inhibitors. Conversely, when proviral DNA is synthesized upon partial failure of RT inhibitors, protease inhibitors may act at a later stage of the replication cycle.

What is the best divergent therapy combination? There is no simple answer; however, presently we favor the combination of zidovudine with lamivudine, associated with a protease inhibitor. The choice of the protease inhibitor lies between the MK-639 (Indinavir), ABT-538 (Riton avir) and saquinavir compounds with the first two presenting an advantage in terms of bioavailability. Combinations of other nucleoside analogues or of a nucleoside analogue with a NNRTI in association with a protease inhibitor should also be explored. Combinations of four drugs may present benefits in terms of efficacy but possibly at the price of increased drug-induced toxicity and reduced compliance.

An initial treatment period of at least one year is probably needed to deplete significantly the reservoir of latently-infected cells. Decisions whether to discontinue treatment or to switch to another combination of drugs will rely on patient's wish, drug tolerance and laboratory tests (viral load, CD4 + count, emergence of drug-resistant mutant viruses). These laboratory data will allow individual tailoring of therapy and give the opportunity to evaluate the best up-to-date drug combinations. Another simple operational way would be to stop therapy after one year and to stick to the goal of transforming PHI patients into long-term non-progressors. Therapy could be reintroduced when immunological and virological deterioration occur.

In conclusion, treatment of PHI patients provides a unique opportunity to change the long-term prognosis of newly-infected patients.

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