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Short communication

Role of animal models in selecting antiviral combinations for clinical studies

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Abstract

Although experimental viral infections in animals have been used extensively in the development of antiviral drugs used as monotherapy, they have not been utilized widely for evaluation of combination chemotherapy. One of the major reasons for the lack of use of animal models is that for the diseases that are the main target for combination therapy, AIDS and hepatitis B and C infections, there is a lack of suitable models for these diseases. In contrast, most combination studies in animal models have been directed against herpes simplex virus infections but there are relatively few patients available who would benefit from combination therapy over single agent therapy. In between those two extremes are the cytomegalovirus infections. While there are animal models available that have been predictive of efficacy in humans and there are sufficient patients available, the use of antiviral combinations in animal models and in humans have begun only recently. At the present time there is not enough information available to establish the predictability for any of the animal models for efficacy of combinations of antiviral agents.

Keywords: Animal models; Combination antiviral therapy

The use of animal models has become a very important part of the preclinical evaluation of antiviral drugs and whenever feasible, new therapeutic modalities should not be introduced into humans without first demonstrating efficacy in an appropriate animal model. There are both advantages and disadvantages to the use of animal models and these are listed in Table 1. Because of lack of convincing efficacy or development of resistance during monotherapy, the use of combinations of two or three antiviral drugs has been proposed or utilized in an attempt to increase the efficacy of antiviral therapy in certain chronic infections such as acquired immunodeficiency syndrome (AIDS), hepatitis B and C and cytomegalovirus (CMV) infections. Other candidate infections for combination chemotherapy include drug resistant herpes simplex virus (HSV) infections in the immunocompromised host.

A list of selected animal models for human viral diseases is shown in Table 2. The development of animal models for AIDS has been particularly

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difficult because the causative agent, human immunodeficiency virus (HIV), does not infect experimental animals, and most surrogate viruses of rodents are somewhat dissimilar to HIV and do not produce a disease that resembles AIDS in humans. The two models that do produce a similar disease, simian immunodeficiency virus (Gardner, 1991) and feline immunodeficiency virus (Zeidner et al. 1990), do not lend themselves well to evaluating combinations due to the size and cost of non-human primates and cats. Although one can choose from four nucleoside inhibitors of reverse transcriptase and a variety of non-nucleoside reverse transcriptase inhibitors, protease inhibitors, interferons, cytokines and other immunopotentiators, few combinations have been tested in animal models, as human studies appear to be easier and faster to perform.

There are a number of animal models for herpes simplex virus infections that are predictive for treatment of encephalitis, neonatal herpes, ocular herpes, genital herpes and cutaneous herpes using acyclovir or adenine arabinoside (Kern, 1990; Bernstein et al. 1993; Ellis et al. 1989). While there have been numerous studies in these models using combinations of nucleosides and interferons, there have been few controlled studies in humans using drug combinations for these diseases (Safrin et al., 1993). Animal studies that have been conducted using combinations of antiviral drugs for HSV infections suggest that a combination of Acyclovir and antibodies should be evaluated in human HSV infections, particularly neonatal herpes.

Another herpesvirus, cytomegalovirus, is an increasingly serious problem in AIDS and transplant patients and there are surrogate animal models in mice, rats and guinea pigs that have been predictive for efficacy of ganciclovir, foscarnet and cidofovir in humans (Dieterich et al. 1992; Freitas et al. 1989; Rubin et al. 1989; Kern, 1991) . Currently, studies in both animals and humans using combinations of ganciclovir, foscarnet and antibodies are in progress.

Table 1
Are animal models useful for predicting efficacy of antiviral combinations

Advantages
1. Animals are complete creatures with similar biological and physiological systems as humans.
2. Murine models have been predictive for some human diseases (HSV, CMV, Flu).
3. Using murine models, a suitable number of combinations can be used so a rigorous, meaningful analysis can be obtained.
4. Synergistic toxicity as well as synergistic efficacy can be determined.
Disadvantages
1. Animals may have drug absorption, distribution, metabolism and excretion characteristics that differ markedly from humans.
2. Most models use surrogate viruses that often produce a disease that is different than seen in humans.
3. Surrogate viruses often have little homology or replicative machinery that is the same as the human virus.
4. In non-rodent models, only small numbers of animals can be used — generally insufficient for testing combinations.
5. Too time consuming, large numbers of patients are in critical need of effective therapy.

Table 2
Animal models for selected human viral infections

A. Human Immunodeficiency Virus
1. Simian Immunodeficiency Virus
2. Feline Immunodeficiency Virus
3. HIV in murine chimeras (thy-liv implants, PBL)
4. HIV — transgenic mice
5. Murine retroviruses
B. Hepatitis B virus
1. Woodchuck hepatitis B
2. Duck hepatitis B
C. Herpes simplex virus
1. Mice — Encephalitis
— Neonatal herpes
— Genital herpes
— Cutaneous herpes
2. Guinea pigs — Neonatal herpes
— Genital herpes
— Cutaneous herpes
3. Rabbits — Ocular herpes
— Cutaneous herpes
D. Cytomegalovirus
1. Murine
2. Rat
3. Guinea pig
E. Influenza virus
1. Mice

At the present time, there are not enough data on the efficacy of combination antiviral therapy in both animals and humans to establish the predictability of any animal model for the outcome of therapy with antiviral combinations in humans; however, we hope that will change in the near future.

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