PMPA Update (8/14/96)

As you may know, an experimental drug called PMPA has received a good deal of media attention based upon postive findings from studies of S.I.V. (simian immunodeficiency virus) in monkeys. PMPA is one of a class of antiviral drugs, known as nucleotide analogues. Like AZT and other nucleoside analogues, they inhibit reverse transcriptase. Gilead Sciences, the developer of PMPA, says that unlike nucleoside analogues, PMPA is already activated; it can enter uninfected cells and form a reservoir of drug that pre-arms them against the virus; in contrast, AZT and drugs in its class work only in cells that have the machinery to activate the drug.

The data and information so far made available has been based upon animal and in vitro data, so it is preliminary. Drugs have looked good before in early testing, only to be disappointing in later clinical trials in humans. It is possible that PMPA has unexpected toxicities not yet revealed. But, it is important to be properly informed about potential therapies.

Gilead is planning for phase I human trials to begin. Below is an update of the phase I plans being made for PMPA; which is followed by a brief review of some of the preliminary data previously made available for PMPA's use both as an antiviral for HIV and for its application in potentially preventing sexual transmission of HIV.

PHASE I HUMAN TRIAL OF IV AND ORAL DRUGS
By the end of 1996 Gilead Sciences plans to begin a phase I test of concept study of their IV formulation of PMPA. HIV+ study subjects will receive a single dose followed by 1 week's observation; and then they will receive once daily dosing for 7 days; safety, antiretoviral effect and pharmacokinetics data will be collected.

Gilead reports they have found that PMPA has a long intracellular 1/2 life of 35 hours in monkeys and 30 hours in human cells in vitro. It is hoped that this long half-life will allow for relatively less frequent dosing than with the administration of currently used antiretrovirals.

A lead candidate for an oral pro-drug of PMPA has been selected and will be studied during the next several months. PMPA taken orally will not be adequately absorbed, but it is expected that the pro-drug will have better absorption; this lead candidate has displayed 40% bioavailability in dogs. A pro-drug is one that will turn into PMPA after it enters the human body. Soon, toxicology in rats and dogs will be studied. If all goes according to plan with the phase I IV formulation, it is expected that it will be followed closely with additional human studies of the IV formulation and/or a phase I study of the oral pro-drug of PMPA.

STUDY OF NEWLY INFECTED MONKEYS
Data was published in Science November 1995, from a study of PMPA given (in two different doses) subcutaneously to 25 macaque monkeys either before or after exposing the monkeys to to S.I.V. *(**Ed. note**: you can search for the article from this page.)* The

monkeys received once daily injections of PMPA for 4 weeks , beginning either 48 hours before, four hours after or 24 hours after inoculating the monkey with SIV. The monkeys were followed regularly for 56 weeks, but no evidence was found of SIV, SIV DNA, or SIV-specific antibodies in the plasma or peripheral blood mononuclear cells (PBMC). From three weeks post-exposure onward, all 10 placebo-treated monkeys became infected with SIV. Each monkey also had a groin lymph node biposied 16 to 26 weeks after SIV exposure. None of the treated monkeys, but all that received placebo, showed evidence of SIV infection in the bipsied tissues. Gilead reported there were no adverse side effects caused by PMPA.

The results of this study imply application of PMPA to post-exposure HIV prevention (such as from an accidental needle stick), and may have implications for use in pediatric AIDS because it is thought that most neonatal HIV transmission occurs during the birthing process.

Again, it is important to remember that these results may not be applicable when PMPA is administered to humans. The Phase I trials in humans expected to start by the end of 1996 will begin to offer more reliable safety and efficacy data.

CHRONIC INFECTION AND PREVENTING SEXUAL TRANSMISSION

At the Ninth International Conference on Antiviral Research in Fukushima, Japan during May of 1996, Gilead presented data on two additional applications of PMPA in monkeys previously infected with SIV.

In one study, ten monkeys that had been infected with SIV for at least 19 weeks were treated with once-daily injections of PMPA for four weeks. After 2 or fewer weeks of treatment, PMPA (30 or 75 mg/kg/day) reduced SIV levels by more than 99% or approximately 2 to 3 logs; some levels decreased below the limit of detection. In the two control monkeys who did not receive PMPA, SIV viral load did not decrease. After the 4 weeks of PMPA treatment ended the SIV viral load rebounded within two weeks back to their baseline levels. It was reported that PMPA was well tolerated in the 30 mg/kg/day dose group. In the 75 mg/kg/day dose group, no clinical toxicities or side effects were observed but chemical changes in blood markers were seen (red blood cell, phosphate and hemoglobin counts went down but were reversible).

In the other study, PMPA was administered in a topical gel intravaginally, and prevented the transmission of SIV to female monkeys exposed intravaginally to the virus. All of the PMPA-treated monkeys showed no signs of SIV transmission or infection throughout an eight-week follow-up period. The control monkeys who did not receive PMPA showed signs of SIV transmission and infection within two weeks of exposure to the virus.

Pending positive results from Phase I human trials, PMPA can be studied both in combination with other HIV antivirals and possibly as a monotherapy treatment, because from in vitro studies of monkeys PMPA resistance was not detected.

The study of the topical formulation of PMPA for prevention of transmission has some obstacles. It will be difficult to decide the type of formulation that may be best suited for widespread use; the PMPA concentration in the formulation must be decided; the timing

of the application needs to be determined; there are concerns about vaginal mucosa irritation that need to be addressed. After initial animal studies, designing appropriate human trials may be complicated. It may be more effective to conduct initial trials in countries where sexual transmission rates are high in identified populations.

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