

MEMORANDUM

DATE: February 3, 2003

TO: Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee

FROM: Working Group on Antiretroviral Drug Development in HIV-Infected and Exposed Neonates, Division of Pediatric Drug Development and Division of Antiviral Drug Products

THROUGH: Shirley Murphy, M.D.
Director, Division of Pediatric Drug Development

Debra Birnkrant, M.D.
Director, Division of Antiviral Drug Products

SUBJECT: Background package for March 3, 2003 Advisory Committee

Introduction:

On March 3, 2003, the committee will be asked to consider issues pertaining to antiretroviral drug development in neonates born to HIV-infected mothers. The Division of Antiviral Drug Products encourages the study of all antiretroviral drugs in HIV-infected and HIV-exposed neonates. However, the rate of perinatal HIV transmission in the United States has declined dramatically, and conducting clinical trials of antiretroviral drugs in HIV-infected and exposed infants is difficult. In addition, the ethics of studying experimental drugs with sometimes significant toxicity profiles in neonates who may not be HIV infected must also be examined. For these and other reasons, the Division of Antiviral Drug Products and Division of Pediatric Drug Development believe there is a pressing need for an open discussion of issues relating to antiretroviral drug development in this patient population.

Perinatally Acquired HIV Infection:

According to the latest statistics from the Centers for Disease Control and Prevention, there are 2,499 children less than 13 years of age with AIDS currently living in the United States.¹ Approximately 3,923 additional children are HIV-infected but have not yet been diagnosed with AIDS; however, since reporting of HIV-infected persons is not mandatory in all states, the actual number of HIV-infected children is undoubtedly higher. HIV-infected children who require treatment usually receive a combination of antiretroviral drugs from different classes in an attempt to keep plasma HIV RNA levels undetectable. FDA has approved 17 antiretroviral drugs in three classes for the treatment

of HIV in adults; 11 of these have been approved for use in children including six antiretroviral drugs that have been approved for use in children younger than one year of age.

More than 90% of HIV-infected children have acquired HIV from their infected mother either in utero or during the perinatal period, and HIV infection can be definitively diagnosed in most infants by one month of age. The current U.S. Public Health Service (USPHS) guidelines recommend treatment of all HIV-infected infants less than one year of age with a combination of antiretroviral drugs as soon as possible after diagnosis because of the high risk of disease progression in this age group.

Ideally, infants born to HIV-infected mothers should have a virologic test (HIV culture or DNA or RNA assay) within 48 hours of birth; this allows for the prompt diagnosis of in utero acquired HIV.² A positive result should be confirmed by a second virologic test as soon as possible. Repeat testing at 14 days of age or by no later than one to two months of age should be considered for all neonates of HIV-infected mothers with a negative test at birth.

Early detection of HIV infection in infants is only possible when pregnant women receive adequate prenatal care including HIV testing and counseling during pregnancy. The FDA has approved only one antiretroviral (zidovudine) for use during pregnancy to prevent the perinatal transmission of HIV. This approval was based on the results of PACTG 076, a landmark study in which 363 HIV-infected pregnant women were randomized to receive either oral zidovudine or placebo starting after 14 weeks of gestation and continuing through labor until delivery as intravenous zidovudine or placebo.³ The newborn infants then received either oral zidovudine or placebo for 6 weeks after birth. The rate of HIV transmission from mother to infant was 7.6% in the zidovudine arm compared to 22.6% in the placebo arm. Shortly after the results of PACTG 076 were known, a U.S. Public Health Service Task Force prepared guidelines for the use of zidovudine in HIV-infected pregnant women.⁴

Current USPHS guidelines have incorporated new information on HIV pathogenesis and treatment and additional data from clinical trials of the prevention of mother to child transmission of HIV. These guidelines now recommend continuation of antiretroviral therapy during pregnancy for pregnant HIV-infected women who are on treatment. In addition, the guidelines recommend that pregnant HIV-infected women who have not received prior antiretroviral therapy receive zidovudine regardless of their plasma HIV level and that additional antiretroviral treatment should be determined by the viral load. (The attached guidelines provide a complete discussion of the treatment of HIV-infected pregnant women). The guidelines also recommend that all neonates born to HIV-infected mothers receive zidovudine for six weeks after birth. Some infants born to mothers with zidovudine resistance or with HIV disease progression during pregnancy may also be treated with other antiretroviral drugs, but the benefits of using most other antiretrovirals for the prophylaxis of HIV infection in the neonatal period are unknown.

Due primarily to the success of zidovudine and other antiretroviral drugs in the prevention of mother to child transmission, the rate of HIV transmission in the United States has dropped to 1 - 2% in HIV-infected mothers receiving care. Estimating how many infants in the U.S. acquire perinatal HIV infection annually is now difficult, though several experts estimate that 300 to 400 HIV-infected neonates are born annually in the United States.

Unfortunately, success in reducing perinatal HIV transmission has largely been confined to the developed world. In contrast, approximately 600,000 HIV-infected infants are born annually worldwide, and most of these children reside in resource poor countries.⁵ Several areas of the world are making measurable progress toward reducing perinatal HIV transmission. For example, prevention programs in Thailand have reduced the rate of perinatal transmission to 6%. Programs are also in place in Brazil, Angola, Kenya, Malawi, and Tanzania.

Issues involving Research in Children and Neonates

The majority of drugs available in the United States are not labeled for use in children. While many drugs are used in children, use is often “off-label” and not based on adequate studies of drug efficacy, safety, and pharmacokinetics in children. Children are not miniature adults and may metabolize drugs at different rates compared to adults or may have adverse events that were not seen in the adults.

At times the use of drugs without adequate information has had disastrous results. Examples include the occurrence of aplastic anemia following treatment with chloramphenicol and dental staining following treatment with tetracycline. Pediatric administration of a drug without adequate pediatric studies can therefore be more of a risk than participation in a well-designed clinical trial. Pediatric patients have a right to receive drugs that have been properly evaluated for their use. The Food and Drug Administration encourages the study of drugs in children of all ages in order to determine the safety and efficacy of drugs in pediatric patients and promote optimal therapy based on pediatric clinical studies and pediatric labeling.

Drug development programs should include pediatric studies when pediatric use is anticipated. However, the FDA recognizes the difficulties involved in the study of drugs in children. At times, ethical issues, such as the weighing of benefits and risks, complicate the design and conduct of drug studies in children. The risks and benefits for children must be calculated whenever pediatric research is conducted. In pediatric research, benefit usually implies that the child has the disease under study or is susceptible to the disease under study; therefore, the disease course and treatment must be completely understood to correctly determine risk and benefit. When research participation offers the prospect of direct benefit to the child, some risk is justified, but that risk should be balanced by the anticipated benefit.

Participation in pediatric studies may provide little benefit to the individual child but provide information that could benefit children in general. When little or no direct

benefit to the individual child is expected, the risks to the child should be no greater than a minor increase over minimal risk; the procedures and experiences associated with participation in the study should be consistent with the child's actual expected care. Local Institutional Review Boards play an important role in the identification of risk and benefit of specific studies in children. Additional information on the ethical conduct of research in children can be found in The American Academy of Pediatrics position statement, which is attached, and the Code of Federal Regulations (45 CFR Subtitle A: 46.401-46.409).

Additional issues must be addressed in any discussion of research conducted during the neonatal period. There has been much debate on the issue of obtaining informed consent for the study of neonates. Neonates are not able to provide assent, and some ethicists argue that the parents of a neonate are not equipped to decide what is in the best interest of their child. There are also practical concerns in the conduct of studies during the neonatal period. For example, venipuncture in newborns can be technically difficult, and the small neonatal total blood volume limits the amount of blood that can be obtained during a study. In addition, the feeding patterns of a newborn can add to the difficulty of studying drugs in which diet affects pharmacokinetic parameters.

Pediatric Exclusivity

Pediatric exclusivity is an economic incentive developed by Congress to encourage pharmaceutical manufactures (the sponsor) to conduct pediatric studies. This incentive provides an additional six months of marketing exclusivity (i.e., no generics can be approved) if the sponsor conducts the studies requested by FDA in a Written Request, submits them within the specified timeframe, and the studies fairly respond to the Written Request. A Written Request outlines the studies FDA believes are necessary to provide a meaningful health benefit in the pediatric population. Thus far, FDA has issued more than 250 Written Requests and requested more than 600 studies in Written Requests. As a result, more than 70 drugs have been granted pediatric exclusivity, and almost 50 drugs have new labels with pediatric information based on the results of studies outlined in a Written Request.

The Division of Antiviral Drug Products has issued 19 Written Requests for the study of antiretroviral drugs in pediatric patients (see the attached template for the Division's Written Request for antiviral drugs). The Division has determined that HIV is similar in children and adults so efficacy studies are not required in children but efficacy may be extrapolated from studies in HIV-infected adults. However, for pediatric labeling, additional pharmacokinetics and safety data must be obtained from HIV-infected children. In its Written Requests, the Division requests studies in HIV-infected children and in infected or exposed neonates in order to determine the safety, pharmacokinetics, and appropriate dose for an antiretroviral drug in children of all ages. The requested studies typically include multiple dose pharmacokinetic and safety studies in HIV-infected children of all ages and HIV-exposed neonates. Patients often receive the antiretroviral drug under study for as many as 14 days in order to determine

pharmacokinetic parameters at steady state. Safety studies in older HIV-infected children are often 24 weeks in duration.

As previously stated, the Division currently requests studies in HIV-infected or exposed neonates. This allows determination of safety, pharmacokinetics, and dosing in children as early as birth. The current USPHS guidelines recommend beginning treatment of HIV-infected children younger than one year of age as soon as possible after diagnosis, so information about the optimal use of antiretroviral drugs is vital for this population. Currently, HIV-exposed neonates without documented HIV infection receive zidovudine as prophylaxis for six weeks after birth and do not receive antiretrovirals after that time. Therefore, neonates later identified as uninfected will derive little individual benefit from participation in a study of antiretroviral drugs. There may be significant risk involved in the study of antiretroviral drugs. Adverse events that have been associated with antiretroviral drugs used in children include hypersensitivity reactions, anemia, hyperbilirubinemia, and events related to mitochondrial toxicity such as peripheral neuropathy, pancreatitis, and hyperlactatemia. The Division has recently begun to re-evaluate the ethical issue of giving experimental drugs with sometimes significant toxicity profiles to neonates who may not be HIV infected.

To date, studies in neonates and young infants have been accomplished primarily through the mechanism of the Written Request. As more antiretroviral drugs are being developed with different safety profiles, different dosing schedules, and different modes of administration, should every drug under development be studied in neonates?

Recently sponsors of antiretroviral drugs have raised valid questions about the feasibility of conducting drug studies in neonates. Since the rate of perinatal HIV transmission in the United States has fallen to 1 –2%, is it possible to recruit an adequate number of HIV-infected and exposed patients for study?

This meeting of the Pediatric Subcommittee of the Anti-Infective Drug Advisory Committee has been convened to consider these issues and the attached questions. Attached are the draft agenda and the questions for the meeting. Also included are several articles focusing on the issues to be discussed. Please review these materials to prepare for what we anticipate will be a thorough and vigorous discussion. We look forward to your contribution to this thought-provoking and productive meeting.

Questions

1. Since neonates born to HIV-infected mothers may be tested for HIV infection in the first 48 hours and at 4 weeks, HIV-infected infants can be diagnosed as early as one month of age. The U.S. Public Health Service guidelines recommend treating HIV-infected infants less than one year of age with combination antiretroviral as soon as possible after diagnosis. All HIV-exposed infants are treated with prophylactic antiretroviral(s) for six weeks after birth.
 - Should only HIV-infected neonates be studied?
 - Is it ethical to study antiretroviral drugs in HIV-exposed neonates, most of whom are not infected? What is the benefit to the uninfected child?
2. Given that an estimated 300 to 400 HIV-infected infants are born annually each year in the United States, that some of these infants are diagnosed after the first several months of life, and that it is difficult to enroll neonates in studies,
 - Are too few HIV-infected infants born annually in the United States to justify asking for studies in this population?
 - Is FDA asking sponsors to study antiretroviral drugs in resource poor countries because there are so few HIV-infected infants in the United States? If so, is that appropriate?
 - If studies are conducted in resource poor countries (where the rate of underlying diseases, malnutrition, infant mortality, and pharmacogenetics, etc. may differ substantially from the U.S.), can we extrapolate results from these studies to the US population?
3. Should we continue to request pharmacokinetic and safety studies for every antiretroviral drug under development?
4. If not:
 - What should the criteria be for deciding which drugs should be studied (e.g., new class, resistance profile, safety issues, pharmacokinetic parameters)?
 - Who should develop these criteria and who should make the decision?

References

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