CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ANTIVIRAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 07/14-16/97

SUMMARY MINUTES

Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ANTIVIRAL DRUGS ADVISORY COMMITTEE

July 14-16, 1997
Armory Place, Silver Spring, MD

Antiviral Drugs Advisory Committee
Scott M. Hammer, MD, Chair
Wm. Christopher Mathews, MD, MSPH
Pamela Diaz, MD
Judith Feinberg, MD
Wafaa El-Sadr, MD
James J. Lipsky, MD

Ermona McGoodwin, Acting Executive Secretary (7/14)

FDA SGE Consultants
John Modlin, MD (7/14-15)
Fred Valentine, MD (7/14-15)
Vernon Chinchilli, PhD (7/14-15)
Joel Verter, PhD (7/14-15)
Janet Elashoff, PhD (7/16)
Brian Wong, MD (7/16)

FDA Guests
Mark Harrington (7/14-15)
Brenda Lein (7/14-15)
Virginia Kan, MD (7/16)

FDA Participants
David Feigal, MD, MPH
Donna Freeman, MD (7/14-15)
Mark Goldberger, MD, MPH (7/16)
Jeffrey Murray, MD
Michael Elashoff, PhD (7/14-15)
Paul Flyer, PhD (7/14-15)
Lauren Iacono-Connors, PhD (7/14-15)
Joyce Korvick, MD (7/16)
Thomas Hammerstrom, PhD (7/16)

These summary minutes for the July 14-16, 1997 Antiviral Drugs Advisory Committee meeting were approved on 9/18/97.

I certify that I attended the July 14-16, 1997 Antiviral Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

Rhonda W. Stover, RPh
Executive Secretary

Scott M. Hammer, MD
Chair

The July 14-16, 1997 meeting of the Antiviral Drugs Advisory Committee consisted of three open session days. On July 14 and 15, 1997, the committee discussed the utility of plasma human immunodeficiency virus (HIV) RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection. On July 16, 1997, the committee discussed NDA 50-740, AmBisome® (liposomal amphotericin B, Fujisawa, USA), as empirical therapy for presumed fungal infection in febrile neutropenic patients.

MEETING PROCEEDINGS-OPEN SESSION-JULY 14, 1997

Topic: The utility of plasma human immunodeficiency virus (HIV) RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection.

Approximately 350 persons were in attendance. A briefing memorandum from the FDA was the only background material sent to the committee prior to the meeting.

Call to Order

The meeting was called to order by Dr. Scott Hammer, Chair, at 8:30 a.m. The committee members, guests, and the FDA participants at the table introduced themselves.

Conflict of Interest

The conflict of interest statement was read by Ermona McGoodwin, Acting Executive Secretary. General matters waivers were granted to all committee participants with interests in companies or organizations that could be affected by the committee's discussion of the meeting topic.

Introduction

Dr. David Feigal, Director, Office of Drug Evaluation IV, FDA, reviewed the history of surrogate markers and the accelerated approval of HIV medications. The purpose of this cooperative meeting was to examine the effects of HIV medications on viral load and treatment response issues.

Presentations-HIV RNA Assays

Lauren Iacono-Connors, PhD (FDA), gave an overview of HIV-RNA measurements. Don Brambilla, PhD (New England Research Institute), discussed the assay characteristics of the Chiron ES bDNA, Organon Teknika NASBA, and Roche Amplicor HIV Monitor assays. Winston Cavert, MD (University of Minnesota), presented data on the comparative tissue compartment activity for plasma RNA and lymphoid tissue RNA.

Presentations-Review of Pediatric Data

Lynne Mofenson, MD, (NICHD), presented the natural history of HIV infection in pediatric patients. Paul Palumbo, MD (University of Medicine and Dentistry of New Jersey), discussed the virology data from the ACTG study 152. The virology data from the ACTG study 300 was given by George Johnson, MD (Medical University of South Carolina).

Open Public Hearing

The following 7 open public hearing speakers presented data, information, and views to the Committee on the meeting topic and other HIV treatment issues. The speakers were requested to make presentations of approximately 5 minutes and to disclose their financial associations.

- Victor DeGruttola, PhD, Harvard School of Public Health
- David Scondras, Search for Cure, Boston, MA
- Alan Norburn, AIDS Treatment Project, London, England
- Francois Houyez, European AIDS Treatment Group (EATG), Paris, France
- Bill Bahlman, ACT-UP, New York
- Iris Long, PhD, ACT-UP, Mount Sinai ACTG-CAP
- Ronald Baker, San Francisco AIDS Foundation, (BETA)

Presentations-Clinical Confirmation of HIV-RNA Changes

After a review of the current antiretroviral guidelines by Sherilyn Stanley, MD, (NIAID), the presentations on clinical confirmation of HIV-RNA changes were introduced by Jeffrey Murray, MD (FDA). Dr. Murray gave the rationale for the agency's decision to explore plasma HIV-RNA as a clinical endpoint in HIV trials. Plasma HIV-RNA as a clinical endpoint would be less complex than current endpoints, more reflective of current medical practice, and allow treatment switches before clinical failure. However, the agency must be confident that HIV-RNA reduction is associated with a decreased clinical progression rate as well as other related issues.

Ian Marschner, PhD, (Harvard School of Public Health/ACTG) presented a cross-protocol analysis of 7 ACTG studies (116A, 116B/117, 175, 197, 229, 241, 259) involving a variety of treatment regimens. After an introduction by Lynn Smiley, MD (GlaxoWellcome), Ralph DeMasi, PhD, (GlaxoWellcome) discussed data from 6 controlled trials (CAESAR, NUCA3001, NUCA3002, NUCB3001, NUCB3002, AVANTI-01) of ZDV+3TC (67%) versus control treatments (33%).

Christy Chuang-Stein, PhD, (Pharmacia and UpJohn), presented combined data from studies 0017 (DLV+ddI versus ddI) and 0021 (DLV+ZDV versus ZDV). Data from the intent to treat population of trial NV14256 (ddC, saquinavir, and ddC+saquinavir) was

given by Lesley Struthers (Hoffman La Roche) and Mike Shear (Hoffman La Roche). Margo Heath Chiozzi, MD (Abbott Laboratories), reviewed data from study M94-247 of ritonavir treated patients.

Michael Elashoff, PhD (FDA), gave a summary of the 5 presentations. Overall, the data that comprised many studies, regimens, and methods of analysis, supported an association between RNA changes and clinical event rates. A reduction of 0.5 log, the smallest decrease studied across trials, was associated with clinical benefit and greater decreases resulted in lower clinical event-rates. Dr. Elashoff stated that there was an association between longer suppression and lower clinical event rates. However, the effect of long-term durability remains to be characterized since durable responses past 24 weeks were rare in these trials.

The committee was given the opportunity to ask questions of the presenters and the FDA representatives. The agency's formal discussion points were posed to the committee on the second day of the meeting-July 15, 1997, after additional presentations and discussion.

The meeting was adjourned at 4:30 p.m. to reconvene at 8:00 a.m. on July 15, 1997.

MEETING PROCEEDINGS-OPEN SESSION-JULY 15, 1997

Topic: The utility of plasma human immunodeficiency virus (HIV) RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection.

Approximately 300 persons were in attendance. A briefing memorandum from the FDA was the only background material sent to the committee prior to the meeting.

Call to Order

The meeting was called to order by Dr. Scott Hammer, Chair, at 8:00 a.m. The committee members, guests, and the FDA participants at the table introduced themselves.

Conflict of Interest

The conflict of interest statement was read by Rhonda Stover, RPh, Executive Secretary. General matters waivers were granted to all committee participants with interests in companies or organizations that could be affected by the committee's discussion of the meeting topic.

Introduction

Paul Flyer, PhD (FDA), stated that the previous day's presentations indicated that there is a strong relationship between the treatment induced changes in HIV RNA and clinical outcome. He discussed the use of HIV RNA as a surrogate marker and its proposed use as a clinical endpoint. The FDA proposes adding a new treatment indication, the suppression of HIV RNA, to serve as the confirmatory trial for a drug approved under accelerated approval. Dr. Flyer stated that the focus of this meeting day would be trial design issues in evaluating HIV RNA response.

Presentations-Viral Changes in Response to Antiretroviral Treatment

The four presentations utilized study data to address issues that included time to virologic response and durability of virologic response. Jeff Chodakewitz, MD (Merck Laboratories), presented data from indinavir protocols 028, 033, and 035. Barry Quart, PharmD (Agouron Pharmaceuticals), discussed Viracept study 511. The results of nevirapine trial BI 1046 were given by David Hall, PhD (Boehringer Ingelheim Pharmaceuticals). The final industry presentation consisted of ZDV+3TC data from 6 controlled trials (CAESAR, NUCA3001, NUCA3002, NUCB3001, NUCB3002, AVANTI-01) and was given by Lynn Smiley, MD (GlaxoWellcome) and Ralph DeMasi, PhD, (GlaxoWellcome).

Michael Elashoff, PhD, (FDA) discussed the design of an RNA-based clinical trial and summarized the four presentations. Dr. Elashoff stated that a primary study endpoint of

time to loss of response could include RNA as well as CD4 and other clinical endpoints. The initial phase of the RNA-based clinical trial could be used for accelerated approval on the basis of percent response and the long-term followup would address the durability of the drugs. Furthermore, the RNA-based clinical trial should allow patients to switch if they do not experience an initial or sustained response and to exit the study, if appropriate.

Dr. Elashoff commented on the utility of the data from the four presentations in defining treatment response for an RNA-based clinical trial. In these studies, a response was considered to be achieving the assay limit, although a less stringent response definition and a flexible loss of response definition may be needed in some trials. The time of response may be as long as 16 to 24 weeks and the time of loss of response may exceed 48 weeks after response.

Open Public Hearing

The following 7 open public hearing speakers presented data, information, and views to the Committee on the meeting topic and other HIV treatment issues. The speakers were requested to make presentations of approximately 5 minutes and to disclose their financial associations.

- Ben Cheng, Project Inform
- Jules Levin, National AIDS Treatment Advocacy Project (NATAP)
- Spencer Cox, Treatment Action Group, New York, New York
- Bill Bahlman, ACT-UP, New York
- John S. James, AIDS Treatment News
- Mike Donnelly, ACT-UP, Golden Gate
- Beverly Dale, Roche Molecular Systems

Charge to the Committee

Dr. David Feigal, Director, Office of Drug Evaluation IV, FDA, discussed HIV trial design issues. He commented on the emergence of individualizing HIV therapy and the need for decision rules versus only following surrogate markers. Dr. Feigal informed the committee that the agency hopes to change product labeling from a label which only states that an agent is approved to treat HIV infection to a label that would describe the performance characteristics of a product.

Committee Discussion

The committee posed questions to the presenters and discussed all the issues that arose from the presentations. The committee was asked by the agency to **comment** (no formal vote) on the following discussion points:

1. Does the available information support our conclusion that a durable reduction in plasma HIV-RNA is evidence of clinical benefit?

Yes, the committee agreed that the data presented suggested correlation between a durable reduction in plasma HIV-RNA and clinical benefit. Several committee members stated that a durable reduction in plasma HIV-RNA predicts (versus is evidence of) clinical benefit.

2. For the purpose of evaluating drug efficacy;

A. What is the most appropriate definition of a clinically meaningful virological response?
B. Should the definition differ for subpopulations such as:
   Children
   Antiretroviral experienced patients or
   Baseline disease status
C. Given this definition what would constitute a loss of that response?
D. How long should responders be followed to assess a durable virologic response?

The committee decided to answer this question grouped as 2A and 2B and 2C and 2D.

2A and 2B
The majority of the committee stated that the definition would vary based on the treatment population. The definitions of a clinically meaningful response ranged from the minimum of a 0.5 log reduction from baseline to a maximum of below quantifiable levels. It was also stated that the definition may have to be a composite inclusive of time to response, CD4 counts, and resistance issues.

2C and 2D
The definition of a loss of response was dependent on the definition of a clinically meaningful virological response. Therefore, the committee's views ranged from an increase to within 0.5 log of baseline to any quantifiable amounts of HIV-RNA. The agency's proposed time to failure was also cited as a reasonable endpoint. The committee agreed that patients should be followed for at least 48 weeks. Additionally, it was suggested that patients be followed 48-52 weeks past the last enrolled patient as the minimum and for as long as possible as the maximum.

3. A. What events should prompt altering randomized therapy during a clinical trial?
   B. Are there circumstances in which this would differ from the virologic endpoint?

The committee stated that there are clinical and immunologic factors that differ from the virologic endpoint that could prompt altering randomized therapy during a clinical trial. Progressive CD4 decline, toxicity, and changes in standard clinical practice were cited as some of these factors. Several committee members cautioned that the therapy switch

criteria be conservative to allow time for the patient to achieve maximal benefit on the randomized regimen.

The meeting was adjourned at 2:55 p.m. to reconvene at 8:30 a.m., July 16, 1997, to discuss NDA 50-740, AmBisome® (liposomal amphotericin B, Fujisawa, USA), as empirical therapy for presumed fungal infection in febrile neutropenic patients.

MEETING PROCEEDINGS-OPEN SESSION-JULY 16, 1997

Topic: AmBisome® (liposomal amphotericin B, Fujisawa, USA), as empirical therapy for presumed fungal infection in febrile neutropenic patients.

Approximately 150 persons were in attendance. Background materials provided to committee members included briefing documents from the sponsor and the FDA.

Call to Order

The meeting was called to order by Dr. Scott Hammer, Chair, at 8:30 a.m. The committee members, guests, and the FDA participants at the table introduced themselves.

Conflict of Interest

The conflict of interest statement was read by Rhonda Stover, RPh, Executive Secretary. It was determined that there was no potential for conflict of interest with the firms regulated by the Center for Drug Evaluation and Research. No waivers were needed for this meeting.

Introduction

Dr. David Feigal, Director, Office of Drug Evaluation IV, FDA, presented a brief overview of ODE IV's reorganization. Dr. Mark Goldberger, Acting Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP), ODE IV, FDA, acknowledged the committee's valuable advice on previous antifungal issues. He informed the committee of AmBisome's review status and requested that the committee give its advice on the empirical therapy indication.

Sponsor Presentation

After a brief introduction by Jerry Johnson, PhD, a general overview of AmBisome was presented by Don Buell, MD. He reviewed AmBisome's structure, mechanism of action, pharmacokinetics, and pre-clinical efficacy. Dr. Buell stated that AmBisome results in much higher plasma concentrations of amphotericin B in animal models and in patients and that it can be tolerated at doses up to 7.5mg/kg/day.

Grant Prentice, MD, discussed the treatment of fungal infections with AmBisome. He presented data from several studies in patients with diagnosed fungal infections. Based on these studies, Dr. Prentice stated that AmBisome can successfully treat patients with invasive mycoses who are unable to receive traditional amphotericin B therapy and that AmBisome has verified therapeutic efficacy against aspergillosis, candidiasis, and cryptococcosis.

Thomas Walsh, MD presented the efficacy and safety data for the sponsor's pivotal trial, Study 94-0-002. In this study, 687 febrile neutropenic patients were randomized to 3.0mg/kg/day of AmBisome (N=343) or to 0.6mg/kg/day of amphotericin B (N=344). Dr. Walsh stated that AmBisome demonstrated equivalence (composite endpoint) to Amphotericin B and that AmBisome was more effective than amphotericin B in preventing proven fungal infection.

The composite study endpoint which determined success consisted of (1) survival for 7 days post study drug (93% AmBisome versus 90% amphotericin B), (2) fever resolved during neutropenia (58% for both groups), (3) no proven or presumed emergent fungal infections (86% for both groups), (4) study drug not prematurely discontinued due to toxicity or lack of efficacy (86% AmBisome versus 81% amphotericin B), and (5) resolution of baseline fungal infection (9/11 AmBisome versus 8/11 amphotericin B). The overall success rate was approximately 50 percent for each medication.

Dr. Walsh also presented safety data to demonstrate that AmBisome substantially reduces infusion related reactions (2.3% to 6.4%). Additionally, AmBisome is significantly less nephrotoxic than amphotericin B (29.4% versus 49.4% at $\geq$ 1.5 times baseline and 18.7% versus 33.7% at $\geq$ 2.0 times baseline) and causes fewer cardiorespiratory and severe adverse events.

FDA Presentation

Joyce Korvick, MD introduced the FDA efficacy and safety presentation. Tom Hammerstrom, PhD presented the statistical analysis of efficacy. He reviewed the study's endpoints and planned analyses, the emergent fungal infections, and AmBisome's other supportive trials. The European studies support the conclusion that AmBisome is at least as effective as amphotericin B.

In the U.S. study 94-0-002, there was an observed difference in favor of AmBisome in the rate of proven fungal infections. For the rate of presumed emergent fungal infections, the difference favored amphotericin B. However, for proven and presumed emergent fungal infections combined (as designated by the investigators), there was no difference in outcome for AmBisome and amphotericin B.

Dr. Korvick further discussed the clinical significance of the discordant results for proven and presumed emergent fungal infections. Although there were a higher number of presumed emergent fungal infections with AmBisome (33 versus 14), the mortality rate in this population was less for AmBisome (12% versus 21%). The mortality rate for proven emergent fungal infections was 46% for AmBisome and 48% for amphotericin B. The mortality rate among patients who did not have emergent fungal infections (proved or presumed) was 5.4% in the AmBisome group compared to 6.7% in the amphotericin B group. Based on the statistical and clinical data, Dr. Korvick concluded that AmBisome is as least as effective as amphotericin B for the empirical treatment of febrile neutropenic patients.

Dr. Korvick also presented the safety analysis for study 94-0-002. She stated that AmBisome has an improved toxicity profile for nephrotoxicity and infusion related reactions. Additionally, Dr. Korvick discussed the pediatric safety profile that was similar to the adult safety profile.

Open Public Hearing

There were no open public hearing speakers.

QUESTIONS TO THE COMMITTEE
(Total votes=8)

1. Is AmBisome safe and effective for use as empirical therapy for febrile neutropenic patients?

VOTE: Yes=8
No=0

The committee agreed that AmBisome was at least as safe, and possibly safer than amphotericin B. The data indicates that AmBisome is less nephrotoxic and has fewer infusion related reactions than amphotericin B. The committee considered AmBisome effective based on it's equivalency to amphotericin B as supported in the data.

2. Please comment on the discordant results for proven and presumed fungal infections in study #002.

The committee agreed that the cause of the discordant results could not be determined based on the presented data. However, several members stated that AmBisome's overall favorable mortality rates and equivalence in proven fungal infections supported the affirmative decision.

3. Please comment on design issues for future trials with particular attention to the endpoint or endpoints which should be given emphasis.

The committee expressed two predominant opinions concerning trial endpoints. Several members favored the composite endpoint while others stated that the primary endpoint should be emergent fungal infection. Additionally, several supporters of the composite endpoint suggested that the safety endpoints should be separate. The committee stated that rigorous, detailed criteria should be established for presumed fungal infections. Other suggestions included the use of diagnostic intensity measures, the followup of patients for 4 weeks past the study period and the obtainment of tissue biopsies and autopsies to confirm outcomes.

The meeting was adjourned at 12:35 p.m.