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PROSPECTIVE DOUBLE-BLIND STUDY OF ZIDOVUDINE
IN EARLY STAGE HIV INFECTION

FINAL REPORT

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FOREWORD

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I. INTRODUCTION:

In late fiscal year 1987 a grant from research area #1 was given to LTC Shannon M. Harrison, Fitzsimons Army Medical Center, Infectious Disease Service as principal investigator to support a collaborative study of Zidovudine in Early HIV Infection. This was an approved protocol through Fitzsimon's IRC, Health Services Command and OTSG HSRRB entitled "Zidovudine in Early HIV Infection". Essentially, R&D Command provided dollars for consumable laboratory studies and travel to support acquisition of data from Denver Health and Hospital civilian patients and FAMC military patients with early HIV infection randomized to either Zidovudine or placebo at 800mg/day. The drug and data collection analysis was provided by Burroughs Wellcome. Only the general results will be reported here and the details of the study design seem adequately covered in the protocol which should be in R&D files.

Because of the salutary response to 12-1500mg of Zidovudine/day in patients treated above 200 CD4 helper cells/mcL in the early phase 2 studies, it was thought that the time to begin ZDV was when patients were between 2-500 helper cells and had at least one symptom (usually lymphadenopathy). Thus they were DOD class 2-5 persons.

It was originally intended to enroll 200 patients randomized between Zidovudine and placebo with the idea that those last randomized would be followed for at least 2 years to try to show a significant difference in progression to severe ARC or AIDS. Severe ARC and AIDS were defined as a combination of the CDC class 4B, C, and D categorizations which fit with the reclassified Department of Defense class 6 definitions. CNS disease was considered an endpoint as was unusual malignancy. The DOD B symptoms were handled as severe ARC in that the individual had to



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have a helper count of less than 200 cells/mcL reproducible for three months and at least two new: weight loss, fever, night sweats, diarrhea, oral candidiasis, oral hairy leukoplakia or multidermatmal herpes zoster.

By the Spring of 1989 there were 110 Zidovudine randomized patients and 108 placebo patients. Sixty-five of these were military and 153 were Denver Health and Hospitals. There had been great difficulty in enrolling enough military patients because of the fact that progression beyond DOD class 2 is generally accepted as reason for medical retirement and many of the patients elected to move outside the Fitzsimons catchment area to continue their medical care. In an effort to get more military patients, secondary sites were begun at Ft. Bliss, Texas; Ft. Hood, Texas; and Ft. McPherson, GA. The military principal investigator saw all of these patients every 28 days and accrued the data and cells.

II. Endpoint/Terminations

Several concurrent large NIH studies looking at similar groups of patients as well as the RAD1/VA/WRAMC study came into safety review in July 1989 and efficacy was detected for Zidovudine in this 2-500 CD4/mcL group. The NIH terminated their studies in early August 1989 and offered everyone active drug at 500mg Zidovudine/day. After careful consultation with DH&H investigators, military investigators and the medical monitor (BG William Moore) it was agreed to unblind the study and offer all persons active Zidovudine 800mg/day. This was approved by all the Institutional Review Committees involved including HSRRB. At that point there had already been 30 withdrawals from Zidovudine and 43 from placebo because of patient's desires to receive known active drug. Another reason for withdrawal besides the forementioned military retirement with movement out of the area was to receive pneumocystis carinii pneumonia prophylaxis when the persons were below 200 CD4/mcL even they were totally asymptomatic.

There were nine endpoints in the Zidovudine group and nine endpoints in the placebo group through mid-September 1989. The "hard" endpoints were evenly divided for pneumocystosis between placebo and Zidovudine, 4:3. The dementia endpoints were more frequent in the placebo 3:1. The mucocutaneous herpes simplex endpoints were more pronounced in the Zidovudine group. Obviously there was no statistical significance.

Secondary endpoints and conclusions from this study were obtained by first analyzing the CD4 helper counts/mcL. There was an average difference of 45 helper cells/mcL between the placebo and Zidovudine group at 8 weeks and about 30 helper cells/mcL at 12 weeks. These were statistically significant. However the statistical difference disappeared by 24 weeks. More importantly analysis of DOD classification starting group for differences in Zidovudine and placebo yielded 28% of those randomized to

Zidovudine starting at class 2 progressed over an average of one year followup. Fifty-five percent of those randomized to placebo starting in DOD class 2 progressed. This was significant at $P < 0.03$. There was a statistical difference in beta-2 microglobulin between placebo and Zidovudine groups at 8 and 12 weeks again. This difference was most marked in those who had significantly elevated beta-2 microglobulins when going on study. There were no statistical differences in CEM cell culture model for HIV virus between the two groups and a very slight statistical difference in the small number of patients who were HIV antigenemic beginning the study.

Toxicity:

There was overall minimal toxicity in this study. The only statistically significant subjective toxicity was nausea where a total of 60% of the Zidovudine patients had severe nausea and only 31% of the placebo patients. However only one patient was taken off study for severe nausea.

Hematologic toxicity was surprisingly minimal at 800mg of Zidovudine/day in that only 2 Zidovudine patients fell below 85gm/L of hemoglobin and no patients showed Grade 4 (<65gm/L toxicity). Analyses for difference between placebo and Zidovudine hemoglobin values at each time interval from 2-60 weeks showed no statistical significance difference by Wilcoxin 2, T test, Kreshkal Wallace test. There was similarly no significant difference between treatment groups in granulocytes or platelet counts although 5 Zidovudine recipients were reported on at least one occasion of <750 granulocytes/mcL compared to no placebo recipients.

Ten of the 80 patients with dose modification went on to permanently discontinue study participation, 8 from Zidovudine, 2 from placebo although not necessarily because of adverse events.

III. Roll Over Portion of Study and Follow On

After Zidovudine patients were continued at 800mg/day and placebo patients were offered open labelled Zidovudine 800mg/day (provided by Burroughs Wellcome on IND held by the Denver Health & Hospitals investigator Dr. David Cohn) there were approximately 150 patients who elected to continue into 1990 and 1991. In September 1991 data was still being accrued on 50 Denver Health and Hospitals patients and 40 military patients. Many of these patients have gone ahead and had DOD 6 events and have had Zidovudine doses reduced or discontinued to start another anti retroviral agent. It was still elected to manage the patients within the framework of accepted Zidovudine practice and collect lymphocytes every 3 months with clinical information. There have been no changes in the toxicity in the last 2 years.

This collection of lymphocytes combined with FAMC's clinical practice lymphocytes for other patients on open labelled Zidovudine, patient's lymphocytes who have moved to ACTG studies at the University of Colorado, and patient's lymphocytes who have moved on to Community Program for Clinical Research in AIDS through DH&H will form an important component of a further collaborative study between WRAIR Retrovirology and FAMC to try to predict antiretroviral resistance and its correlation with clinical events. Commander Doug Mayers at WRAIR Retrovirology has been able to resurrect lymphocytes preserved from this study and FAMC's clinical HIV practice on out to 200 weeks in frozen storage.

IV. Conclusion

Although this study did not achieve the statistical significance for progression to severe ARC/ADS of the larger NIH studies or the VA/RAD1/WRAMC study, it provided a significant portion of the data for Zidovudine safety at 5-800mg/day and showed a very delimited trend toward retardation of DOD class progression which is important and preservation of health of the soldier, dependents and retired DOD health care beneficiaries. The study does further validate ZDV's effect on surrogate markers. ←

The study led to three poster presentations at the 6th International HIV meeting in San Francisco, CA in June 1990 and at least one paper submitted to JAIDS on the surrogate markers. This study's contribution to further WRAIR Retrovirology collaborative studies should be important.