AIDS

Cutter

MILES

GMA-5-070

TO: V. Shalson

DATE: 24 April 85

FROM: G.M. Akin

SUBJECT: TRIP REPORT, INTERNATIONAL SYMPOSIUM ON AIDS, ATLANTA

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XP Report

I left this meeting both dissapointed in that there was no encouraging new information, and depressed in that what new information was available was not good news. Since there were three sessions running concurrently, I attended the sessions on epidemiology and blood/plasma. I believe M. Mozen attended the sessions on virology. Each day there was a plenary session for the first couple of hours. There were also poster sessions which changed daily. It was interesting to note the amount of information about the disease and the virus which has come to light since the first CDC Symposium on AIDS about 2 years ago.

I have a 91 page program with summaries if anyone wishes to read any of the paper and poster presentations.

General Observations

1. Three different experts from Government Agencies (Curran; CDC; Gallo, NIH; Faucci, NIH) more or less intimated that henceforth, government researchers would make available no hope-giving, preliminary research data (which the media blows out of proportion) until evidence for efficacy or accuracy is pretty well established. I got the impression that they have data on protective antibodies and are working on vaccines, but they gave no encouraging remarks or predictions about this.

2. Since 1980, one million Americans in all risk (including "no known risk") categories have been exposed to, ergo potentially infected with, HTLV-III/LAV virus. Best statistical analyses indicate that 330,000 of these will develop AIDS in the next 5 to 10 years.

3. Even with the development of a vaccine, the incidence curve will continue to rise for at least 5 years due to the foregoing exposure, and a vaccine would probably, not be of value in these people. If a vaccine becomes available, ALL the population of the country should be immunized.

4. The incubation period is probably much longer than that which has already been stated. This error could be due to the many people already exposed who have not yet developed the disease, and is weighed on the low side of the bell curve by the ones who developed the disease early.

5. There is no question that AIDS can be heterosexually transmitted both from male to female and female to male. To date, in the U.S., most of these cases have been in New York and involve prostitutes. At present, cases involving no risk factor other than heterosexual relationships account for 1% of total cases.

6. In those with LAS/ARC (lymphadenopathy syndrome/AIDS related complex) who have progressed to full AIDS, the time for development has averaged 28 months, and ranges from 14 months to 57 months.

7. Peter Levine was the keynote speaker for the hemophilia/blood plenary session. He spoke very favorably of heat treated products, but gave ALL the credit to the CDC with not one tiny kudo to industry. He reviewed the difference in the immune profile of the hemophiliac vs. the non-hemophiliac, and stated that as of the symposium, 92% of severe hemophiliacs have become seropositive to anti-HTLV-III. He also stated:

Now that's a "good friend" for you!!

   A. No non-heat treated concentrate should now be used.

   B. AIDS may soon exceed hemorrhage as the major cause of death in hemophiliacs.

   C. In hemophilia patients, the AIDS incidence curve is plateauing, since nearly all hemophiliacs have now been exposed, ergo infected. This being true, and since not all infected hemophilia patients have or will develop AIDS, this may be a good indication that not all exposed individuals in ANY risk group will get the disease.

8. Other points from the hemophilia/blood/plasma session.

   A. As of the meeting, there have been 142 cases of AIDS from blood transfusions.

   B. Neonates develop AIDS after blood faster than adults.

C. As of now, it is thought that transfusion associated AIDS in adults has an incubation period with about a 29 month median, infants 13 months. This could become longer as time passes and further cases now incubating develop.

D. In hemophilia patients who have seroconverted to + for anti-HTLV-III, the time from seroconversion to AIDS has been ± 3 years.

9. Gallo stated that HTLV-III infection is probably for life, since the virus encodes the nucleus of the helper lymphocyte with its RNA, causing each daughter cell of the lymphocyte to also produce virus. The virus, per se, does not cause Kaposi's sarcoma, but predisposes to it.

10. "The Phantom", Arye Rubinstein, was scheduled for a poster session on April 15 on Treatment of AIDS with IGIV in adults. True to his usual elusivity, his board remained blank all day. I later found out from Richard Schwartz that Rubenstein had not attended because he just became a father. A summary of his "poster-which-wasn't" is attached.

11. Lastly, the only somewhat encouraging word that was heard was from Martin Hirsch of Mass General/Harvard who discussed the current status of antiviral agents in HTLV-III therapy. While the work worldwide is very preliminary, mostly less than one year in progress, there are some six agents that look promising with respect to therapy. It is quite possible that since the drugs only seem to work as long as one is taking them, that life-long treatment may be required.

GMA:dmc

Attachment

Monday, April 15

M-67 Poster

IMMUNE STATUS OF PATIENTS WITH KAPOSI'S SARCOMA FROM VARIOUS POPULATION GROUPS. R.Sher* J.I.Phillips. S.Antunes. J.Screwston.

Fifteen patients with Kaposi's sarcoma - 5 heterosexual caucasions, 8 heterosexual blacks and 2 homosexual males - were investigated as to their immune status.β_2-microglobulin levels and antibodies to HTLV-I and III. The heterosexual group, 3 males and 2 females, were all over 60 except for one. Their Tcell subsets,T3,T4,T8,T4: T8 ratio, delayed hypersensitivity skin test (DHS), in vitro transformation to mitogens, immunoglobulins and β_2-microglobulin were normal. The two AIDS Kaposi's sarcoma showed reversed ratios of T4:T8, decreased transformation, absent DHS, and elevated immunoglobulins and β_2-microglobulin. Three of the black heterosexuals showed reversed T4:T8 ratios - one with decreased DHS and 3 with decreased transformation to PHA and PWM. Two patients with normal cell mediated immunity (CMI) had elevated IgG serum levels. Serum β_2-microglobulin was slightly elevated in 2 patients with normal CMI and markedly elevated in one with decreased CMI. All cases were serum negative for HTLV-I. Of 10 cases which were tested for antibodies to HTLV-III, 4 were positive - one heterosexual caucasian, one AIDS Kaposi's and 2 black heterosexuals. This limited study reveals that Kaposi's sarcoma in heterosexual caucasions and in 62.5% of heterosexual blacks, is not associated with defective CMI.

M-68 Poster

Treatment of AIDS with Hyperimmune Serum to Lymphadenopathy Virus (LAV) ARYE RUBINSTEIN*, B KRIEGER, M SICKLICK, L BERNSTEIN, B NOVICK, A WIZNIA.

Six adults with endstage AIDS and opportunistic infections with/without Kaposi's sarcoma were studied. The disease course of all patients was relentlessly progressive with septic temperatures, wasting, leukopenia, lymphopenia, and markedly impaired T and B cell functions. Intravenous gammaglobulin (IVGG) with high antibody titers to LAV was infused biweekly at a rate of 150-500mg/kg/week, for a period of 3-8 months. All patients defervesced within 6 weeks of treatment,gained weight and did not develop new infections. One patient deteriorated after 3 months of treatment following the use of unprescribed high doses of steroids. The pretreatment markedly elevated levels of circulating immune complexes (C1q assay) decreased to normal values in all patients. In one patient high levels of circulating immune complexes recurred after 3 months. The in vitro lymphocyte mitogenic responses to phytohemagglutinin and pokeweed mitogen improved in 2 patients. Absolute numbers of T_4 and T_8 cells and T_4/T_8 ratios did not change significantly. Treatment with hyperimmune IVGG can ameliorate the disease course of AIDS but does not significantly improve immunological competence in end stage disease.

M-69 Poster

Therapeutic Apheresis in Homosexual Men with Inflammatory Polyneuropathy DOBRI D KIPROV*, R LIPPERT, I LIPKIN, D ABRAMS, RG MILLER

A peripheral neuropathy syndrome occurs in some patients with AIDS or the lymphadenopathy syndrome. The presence of circulating antimyelin antibodies and their deposition along myelin sheaths in sural nerve biopsies suggest an immune mediated mechanism. Two homosexual men with the lymphadenopathy syndrome and progressive polyneuropathy, after having failed to benefit from a course of high dose steriods, were treated with plasmapheresis combined with lymphocytapheresis. Clinical improvement of the neurologic symptoms occurred in both patients. Electrophysiologic studies also showed improvement. One of the patients has sustained his improved neurologic status over a 15 month follow up period and the second patient is symptom free 10 months after treatment. Antimyelin antibodies were removed rapidly and remain at low levels during the follow period. There was a 25% decrease in the absolute lymphocyte count during the treatment but no significant change in the helper/suppressor ratios were observed. Two patients with AIDS and advanced chronic progressive peripheral neuropathy were treated with plasmapheresis. Clinical and electrophysiologic studies showed improvement in one of the patients. Our preliminary findings indicate that therapeutic apheresis is a safe and effective treatment for this polyneuropathy syndrome.

M-70 Poster

Pilot Study to Evaluate the In Vivo Effects of Thymosin Fraction 5 (TF5) in Male Homosexuals (Ho) and Hemophiliacs (He) with Impaired Cellular Immunity RICHARD S SCHULOF,* G SIMON, M SZTEIN, J GREENSTEIN, R GALLO, A GOLDSTEIN, et al.

Thirty-two Ho or He with T4/T8 ratios <1.2 were treated with TF5 by daily SQ injection for 10 weeks. Most Ho/He exhibited lymphadenopathy ± constitutional symptoms and HTLV-III seropositivity. Peripheral blood lymphocytes (PBL) from most subjects exhibited depressions of absolute T4+ cells/mm^3, PHA-induced IL-2 production and lymphoproliferative responses in MLR. A battery of immunologic and serologic parameters were repeated at 2,6, and 10 weeks after beginning treatment. Three doses of TF5 were studied in 10 Ho/He each: 30 mg, 60 mg and 120 mg. Two Ho who received 30 mg developed AIDS while on study whereas 2 Ho/He who received 120 mg had to discontinue therapy because of local toxicity. Two-thirds of subjects who received 60 mg had gradual improvements in MLR and IL-2 production if initially depressed. No consistent effects were seen on anti-HTLV titers. TF5 improved the immune functions of many Ho/He but did not generally normalize the baseline T4/T8 ratio, or other surrogate markers for AIDS if they were present prior to therapy including elevations of serum alpha interferon or β_2 microglobulin levels; nor did it influence the presence of AIDS-associated ultrastructural markers if they were detected in PBL prior to treatment.

M-71 Poster

Thymus Transplantation in AIDS and Recurrence of HTLV-III Infection. JM DUPUY*, DD PEKOVIC, H GOLDMAN, C TSOUKAS, N GILMORE, Y THIBODEAU, L PELLETIER, M JOLY, R DUPERVAL.Institut Armand-Frappier,Montreal Childrens,Montreal General,Royal Victoria,Jean-Talon Hospitals,Montreal and Centre Hospitalier Universitaire de Sherbrooke,

Since October 1983, 14 adult patients with AIDS have received one or several thymic grafts. All cases had opportunistic infections and 3 patients also had Kaposi's sarcoma. Thymic tissue from infants undergoing cardiac surgery was cultured for 3 weeks to provide epithelial cells free of lymphocytes and fibroblasts.Cells were injected intraperitoneally or intrahepatically.Clinical and immunological status were assessed monthly. Liver biopsy was performed in 7 cases at the time of grafting and 2 months later.Transplantation was well tolerated in all cases.Six patients died and 8 survived after a mean survival time following transplantation of 8.8 months and 7 months, respectively.Clinical improvement and absence of new opportunistic infections were transient.Partial immunoreconstitution was evidenced by an increase in peripheral blood lymphocytes (12 out of 13 cases) and lymphocyte subsets (8 out of 13 cases) as well as by liver infiltration of T4 and T8 positive cells (5 out of 7 cases).In 5 out of 7 patients, although HTLV-III antigens were not detected in the liver at the time of grafting, double staining IF showed that HTLV-III antigens were present, at the site of the graft 2 months later, in T4+ cells only. Transient immunoreconstitution may,therefore, be related to destruction of newly differentiated T lymphocytes.

M-72 Poster

Phase-I/II Trial of rIL-2 in Patients with AIDS & ARC PETER KERN,* J TOY, B MEIGEL, M DIETRICH

Toxicity and clinical response of recombinant Interleukin-2 (rIL-2) were studied in 6 patients with AIDS and in 6 patients with ARC. Increasing doses from 10^5 to 10^6 U/sq.m. given as an intravenous bolus were tolerated without major toxicity. 4-hour, 8-hour and 24-hour infusions of 10^6 U/sq.m. revealed similar results. Eight patients received daily infusions for up to 14 days. During treatment a rise of body temperature, pulse rate and a decrease of blood pressure was seen approximately 4 hours after start of infusion which continued for a further 9 to 12 hours. Fever and chills could be controlled by paracetamol to some extent. Minor hepatic toxicity was observed. The rise of leukocyte count was due to an increase in lymphocytes and eosinophils. In all cases a pronounced seborrhoic dermatitis was observed. Lymph node size in 3 ARC patients and in one AIDS patient was slightly smaller after the treatment period. Severe diarrhea due to cryptosporidiae ceased in 2 of 3 patients under rIL-2 treatment and did not reoccur in the following 2 months. Thus,the molecular replacement of the deficient lymphokine IL-2 might be of benefit and should be considered in further clinical trials.