10th International Conference on Antiviral Research (ICAR)

April 1997, Atlanta

Report of Pollard's d4T/ddI study in treatment-naive is posted separately on this web site

MKC-442 Preliminary Data follow-up

At the Retroviral Conference in January 1997, Carey Moxham of Triangle Pharmaceuticals reported preliminary data from an initial dose ranging study of MKC-442, a NNRTI. This data is available in a separate report on the NATAP web site.

AT ICAR, data for two additional dose regimens were reported (500 mg once per day and 500 mg twice per day). Those receiving 500 mg once per day (n=6) achieved an initial viral load reduction of about -0.8 log at day 8 which immediately started to rebound towards baseline. Those receiving (n=6) the 500 mg twice daily dose achieved an initial viral load reduction of -1.19 log at day 8; Triangle says 5/6 had >1 log reduction, while 1/6 did not respond well at all; they are investigating why this person did not respond to MKC-442. It is preliminary but only one person taking 500 mg twice daily had follow-up data extended to 29 days, and their viral load reduction of -1.19 was sustained at 29 days. This is unusual and of interest because our experience with NNRTIs is that after an initial relatively profound reduction in viral load, resistance sets in quickly and viral load rebounds towards baseline.

At ICAR, Triangle reported 1/26 suffered serious rash, 12/26 had asymptomatic elevations (>2.5 x upper limit of normal) in liver transpeptidase (liver enzymes). It appears as though twice daily dosing will be selected for future studies, which will explore MKC-442 in a variety of combinations with other drugs. Initially, interaction studies will be conducted to determine dosing, safety, etc.

Vertex Pharmaceuticals' 3rd Generation Protease Inhibitor

In an attempt to improve on potency and cross-resistance, Vertex is researching the development of a 3rd generation protease inhibitor. Their partner in this effort again is Glaxo Wellcome.

Nelfinavir 10-month data follow-up

At ICAR , Sharon Chapman, PhD of Agouron Pharmaceuticals reported 10-month (40 week) follow-up data for study 511. Previously, 6 month data was reported in January 1997 at the Retroviral Conference, and is available in NATAP's 9-page report on nelfinavir on this web site.

	Mean CD4	Mean viral load*	% undetect (500 copies)
NLF (750)+AZT/3TC n=74	+173	-2 log	83%
NLF (500)+AZT/3TC n=65	+174	-1.8 log	60%
AZT/3TC#	na	na	na

* The log reduction in viral load was calculated using the bDNA viral load test with a lower limit of detection of 500 copies. The 2 log reduction in viral load from baseline (for the NLF 750 arm) after 40 weeks was approximately he same reduction achieved in this triple arm at 24 weeks when the same viral load test was used (with a 500 copy lower level of detection). Some of the numbers in this table were taken by visual examination of a graph line chart, and so were approximated. # The participants receiving AZT/3TC alone were permitted additional therapy after the initial 6 month trial period.

Triple Therapy in chronically infected treatment-naive individuals with Nelfinavir+AZT/3TC

At ICAR, Dr. Martin Markowitz of the Aaron Diamond AIDS Research Center, reported follow-up data from research conducted by he and Dr. David Ho. Earlier reports are available on the NATAP web site, but contained in this report is follow-up data of between 10 and 15 months. This study was designed to explore the possibility of eradication in this population and to monitor the effect of the therapy on the "third phase of decay" of HIV (potential sanctuaries sites for the virus outside the peripheral blood: lymph tissue, semen, etc).

Twelve treatment-naive but chronically infected individuals with HIV-RNA above 10,000 copies/ml were treated with open-label nelfinavir+ AZT+3TC. Dosing regimen: 750 mg nelfinavir 3X/day; AZT 200 mg 3X/day; 3TC 150 mg 3X/day. Various virological and immunological monitoring is being used: blood viral load (Chiron bDNA 2nd generation test-500 copies/ml), PBMC co-culture; PCR for ms (multiple spliced) and us (unspliced mRNA and DNA; lymph tissue biopsy at approximately 1 year; semen analysis (11/12); lymphcyte profile including CD4, CD8, CD45RO+ (memory cells), and CD45RA+62L+ (naive cells).

Baseline characteristics:

mean viral load: 209,000 (5.32 log)

median viral load: 81,270 (4.91 log)

range: 17,000-864,000 copies/ml (4.26-5.94 log)

mean CD4: 258

median CD4: 253

range: 37-557

Study Follow-Up

A number of individuals were experiencing some of these relatively minor HIV-related conditions which resolved or improved dramatically during therapy:

- resolution of HIV myopathy
- resolution of hairy leukoplakia in one subject
- near resolution of eosinophilic pustular folliculitis in one subject
- resolution of oral candidiasis in two subjects
- no new HIV related events in all subjects

commentary : resolution of immune system related infections (OIs) may be easier to accomplish the earlier in disease progression that an individual is treated. It is suggested that one good reason for treating early in stage of disease progression, particularly immediately after sero-conversion, with a potent regimen is to catch the immune system before it declines and to prevent such decline. It is also felt that at this early stage of disease progression when the immune system is relatively intact an individual is most likely to be most responsive to therapy, in terms of preserving the immune system, having a maximal antiviral response and sustaining that response. It is this theory, among other reasons, that is leading some researchers to suggest that eradication of HIV *may be possible* if an individual is treated early enough. Of course, research is ongoing exploring eradication and the other theories mentioned above and it is too soon to draw any conclusions.

Safety and Tolerability:

- 1/12 discontinued therapy due to diarrhea, abdominal pain and grade 4 elevation of CPK
- no other grade 3 or 4 toxicities
- diarrhea and asthenia (fatigue, tiredness) were the most common side effects reported

Viral Load : At 16 weeks, Markowitz reported 11/11 were below 100 copies as measured by the Chiron bDNA 3rd generation test. But, the accuracy and reliability of this test has not yet been as well established as the commercially available tests such as the Roche PCR Amplicor test which measures as low as 400 or 200 copies/ml, or the Chiron bDNA test which measures more reliably as low as 500 copies.

In this analysis following participants out to about 1 year, one individual had a recent

rebound in viral load during therapy and is initially responding to a switch in therapy to ritonavir/saquinavir. This individual's baseline viral load was 865,000 copies/ml and their baseline CD4 was 75.

One subject early in the study was intolerant to study drugs, was switched to d4T/3TC/indinavir, and is tolerant and virologically responsive to new therapy.

Another participant's viral load has been recently fluctuating between under 500 and above 500 copies.

The remaining participants (8/10 excluding the one who was found early in the study to be intolerable) are undetectable as measured by bDNA Chiron test with a lower limit of detection of 500 copies/ml. at about 1 year.

GI-associated lymph tissue. Of 10 evaluable patients followed out to between 10 to 15 months: 9 have <100 copies of msRNA, 8/9 are culture negative, all 10 are proviral DNA positive; 8 have <100 usRNA, the two who have >100 usRNA are also culture positive. (ms--multiple spliced RNA; us--unspliced RNA)

Semen: HIV PCR Mononuclear Cells. Data from 4 evaluable subjects followed out to 13 months was reported and have <100 msRNA and usRNA, but are proviral DNA positive.

The significance of being proviral DNA positive is open to interpretation. At the January 1997 Retrovirus Conference, it was reported that the proviral DNA in these individuals was decaying but at a slower rate.