National AIDS Treatment Advocacy Project

Report From ICAAC - Day One 9/16/96

This is Jules Levin reporting from ICAAC (Interscience Conference on Antimicrobial Agents And Chemotherapy) in New Orleans. Last night was a satellite meeting with Pharmacia & Upjohn to discuss their initial results from the interaction studies of delavirdine with saquinavir, ritonavir and indinavir. Today's Late Breaker session included several important presentations. Below are highlights of the important developments from today's session as we usually do from HIV conferences, and upon return to New York a more complete analysis will be reported here.

List of presentations reported below:

1. **delavirdine interaction studies with protease inhibitors**
2. **141W94--initial data for Glaxo's protease inhibitor**
3. **ritonavir+saquinavir combination study--12 week data**
4. **DMP-266, a new NNRTI--initial data**
5. **AIDS progression and survival data from 3TC clinical endpoint study**

1. Delavirdine interaction with protease inhibitors

Initial data from Upjohn's interaction studies have been provided. The studies of delavirdine with each of the 3 approved protease inhibitors were conducted in a small number of HIV- subjects and the results could be considered preliminary. Results in HIV- individuals could be different then for HIV+ individuals. It may be advisable not to make treatment decisions yet until further information is available. It is advisable to consult with your doctor about this issue.

Indinavir blood concentrations are raised by 50% when combined with delavridine. Delavirdine levels remain unchanged. The study was conducted by Upjohn, but Merck did not participate in this study. Merck is reviewing the data for comments. They may conduct their own interaction study. A 50% rise in blood levels of indinavir would necessitate a dose reduction of indinavir. Delavirdine's normal dosing regimen is 400 mg 3X/day. Upjohn suggested that two dose regimens of indinavir could be considered--400 mg tid (3X/day) and 600 mg tid. The current recommended dose of indinavir is 800 mg tid. If using the 400 mg dose of indinavir, that would in effect raise the dose to 600 mg; if using the 600 mg dose of indinavir, that would in effect raise the dose to 900 mg.

Both options raise significant questions. A 600 mg dose of indinavir is below the recommended regimen and raises concern about causing resistance. A 900 mg dose of indinavir is above the recommended dose and could raise the incidence of side effects, in

particular nephrolithiasis (which can lead to kidney stones).

Saquinavir's blood levels were increased 5-fold when used with delavirdine. Delavirdine levels were not significantly altered. There was a 13% incidence of raised LFTs (liver enzymes--ALT) which Upjohn said was reversible, and a 6% incidence of grade III or IV raised LFTs. Upjohn recommended CLOSE MONITORING of LFTs if combining delavirdine with a protease inhibitor. Once a week lab tests of your LFT may be advisable during the initial stages of taking combination. If you have Hepatitis B or C, you may be more likely to experience an elevation of your LFTs.

The interaction study of ritonavir was also in a small number of individuals and used a lower than recommended dose of ritonavir of 300 mg. The recommended dose of ritonavir is 600 mg. Upjohn said their was a non-significant change in delavridine blood levels and no change to ritonavir levels; the recommended dose regimen for delavirdine is 400 mg 3/X day (tid).

Boehringer Ingleheim, the manufacturer of nevirapine, has said down here that saquinavir blood levels are reduced by 37% when combined with nevirapine, but it is not clinically significant. If you are going to combine a NNRTI with saquinavir it appears as though delavirdine is preferable. Interaction studies of nevirapine with indinavir and ritonavir are ongoing.

The CD4 and RNA data in a number of different studies of delavirdine were presented. The efficacy data has similarities to the nevirapine data and will be comprehensively reported here upon return to New York.

As with nevirapine, a mild, moderate or severe rash can occur with use of delavirdine. Delavirdine, like nevirapine and the 3 approved protease inhibitors are processed through the CYT P450 system in the liver. Therefore, there is potential for elevated LFTs.

2. 141W94--the new Glaxo Welcome protease inhibitor

For the first time, Glaxo presented much anticipated preliminary efficacy and safety data for 141. It is based upon a small number of study participants and is only 4 weeks of data. It is too soon to make any judgments about the usefulness of this drug but this initial report is favorable. CD4, viral load and safety data were presented for 4 dose regimens--300 mg bid, 300 mg tid, 900 mg bid, 1200 mg bid. This study is intended to examine safety, tolerance, pharmacokinetics, antiviral activity, CD4; subjects are protease inhibitor naive with CD4 between 150 to 400 cells. Baseline RNA was 4.83 log (I'm guessing now that is about 70,000 copies/ml-I don't have my calculator with me) and baseline CD4 was 280.

The RNA reduction from baseline for the 1200 mg bid dose was 1.95 log at 3 weeks and 1.5 log at 4 weeks. 10 individuals were enrolled in this arm. The CD4 increase was about 125 cells after 4 weeks. The 4-week RNA data was based on 4 individuals. The 1/2 log rebound from 3 to 4 weeks may have been due to one individual's RNA rebound who may have stopped taking drug.

3 individuals had lumbar punctures done to assess CSF penetration. It appears as though

1% of the plasma concentration was present in the CSF. From animal studies, a higher CSF penetration was expected but these results are early.

Preliminarily, 141W94 appears to be tolerable, shows good antiviral activity, study subjects felt good from taking the drug, and the side effect profile was acceptable.

We can expect larger clinical studies to begin this fall.

3. RITONAVIR+SAQUINAVIR

The initial report of the Vancouver data was reported on this NATAP website.

In Vancouver, the initial 6 weeks of efficacy and safety data were presented from this small (about 30 individuals per regimen) pilot open-label study for 2 of the 4 dosing regimens being explored in this study. Those taking 400 mg ritonavir bid + 400 mg saquinavir bid experienced about a 2.14 log RNA reduction and about a 70 CD4 increase from baseline after 6 weeks; about 50% of this group had undetectable RNA (under 200 copies/ml as measured by Roche PCR). Those subjects taking 600 mg ritonavir bid + 400 mg saquinavir bid experienced about a 2.42 log reduction and a 115 CD4 increase from baseline after 6 weeks; about 65% of this group had undetectable RNA (lower limit of measure--200 copies/ml). The side effect profile did not appear to be any different than that for ritonavir monotherapy. The discontinuation rate was relatively low. Refer to the post-Vancouver NATAP report of saquinavir+ritonavir for more comprehensive details.

At this meeting, 12 weeks of efficacy and safety data were presented for the two afore-mentioned dose regimen groups, and 6 weeks of data were presented for 2 additional dose regimen groups. Those taking 400 mg ritonavir bid + 400 mg saquinavir bid experienced about a 2.74 RNA reduction and an 91 CD4 increase from baseline after 12 weeks; about 75% had undetectable RNA (lower limit of measure--200 copies/ml). Those taking 600 mg ritonavir bid + 400 mg saquinavir bid experienced a 3.06 RNA reduction and 113 CD4 increase from baseline after 12 weeks; about 70% had undetectable RNA (below 200 copies/ml). There was a difference in the baseline RNA between these 2 dose regimen groups; this could account for the differential in % undetectable between the 2 groups. The baseline RNA numbers are available in the NATAP post-Vancouver report of this combination.

For the 2 additional dose regimen groups, the first 6 weeks of data were presented. Those taking 400 mg RTV tid (3X/day) + 400 mg tid SQV experienced a 2.09 RNA log reduction and 74 CD4 increase from baseline after 6 weeks; about 30% had undetectable RNA at 6 weeks. Those taking 600 mg RTV + 600 mg SQV experienced a 2.19 RNA log reduction and an 88 CD4 increase from baseline after 6 weeks; about 45% had undetectable RNA (below 200 copies).

The differences between treatment regimens in the above RNA and CD4 responses were not statistically significant. It is still uncertain which of the 4 dose regimens may be superior. The tid regimen appears to cause more side effects and therefore may be the least preferable. But, the efficacy data for all the groups is similar. We do not yet know the longer term durability of these benefits nor the longer term safety profile. Follow-up studies utilizing the combination of saquinavir+ritonavir in 4-drug regimens are planned.

Even a 5-drug therapy may be planned.

Discontinuations-- 9 in total, but 5 from the 400+400 tid group. Individuals taking this tid regimen will be offered a bid regimen. Asymptomatic triglyceride elevations have been observed and ought to be followed for individuals taking ritonavir+saquinavir.

4. DMP-266, a new NNRTI

This double-blind pilot study was meant to evaluate antiviral activity, tolerability, pharmacokinetics of DMP-266 alone and in combination with indinavir. This is the first efficacy data available for this new drug from DuPont-Merck. Of the 16 patients enrolled 11 received DMP-266 monotherapy for 2 weeks and 5 received placebo. 13 subjects were antiretroviral experienced and one was protease inhibitor experienced. After 2 weeks open-label indinavir 800mg tid was provided to all study subjects. 14 weeks of data are presented for both groups--11 subjects added indinavir (IDV) to DMP-266 after 2 weeks of monotherapy with DMP-266, the other group received IDV monotherapy after 2 weeks of placebo.

The mean baseline CD4 was 221 cells and the mean baseline plasma RNA was 131,825 copies/ml.

The dosing regimen for DMP-266 is 200 mg once per day. After 2 weeks of monotherapy with DMP-266, the mean RNA reduction from baseline was about 1.68 log (98% suppression) and the CD4 increase in CD4 was about 96 cells.

After 12 weeks of combination treatment with DMP-266 and indinavir, a mean reduction of 3.20 log. The mean CD4 increases were about 125 cells. 6/11 (55%) subjects receiving combination therapy had undetectable viral load (below 400 copies/ml).

DMP-266 decreased indinavir plasma concentrations by about 37%. No significant changes in DMP-266 pharmacokinetics parameters were observed after addition of indinavir.

No subjects discontinued during study. 4 individuals taking the combination experienced skin reactions; all were characterized as mild. Future studies are being planned.

5. Clinical Endpoint Study of 3TC

This was a double-blind, randomized trial comparing clinical efficacy and safety of 3TC or 3TC+loviride, a NNRTI (LVR) vs. placebo, and conducted overseas. CD4 criteria: 50-250. 1892 study subjects at entry were taking either AZT, AZT+ddI or AZT+ddC and were randomized to add either 3TC (150 mg bid), 3TC+LVR (100 mg tid) or placebo for an intended 52 weeks, as DSMB (Data Safety Monitoring Board) recommended trial termination before reaching 52 weeks.

RATES OF PROGRESSION TO AIDS OR DEATH:

placebo	3TC	3TC+LVR
17%	9%	8%
81/482	80/935	38/475
There was a 54% reduction in progression to 1st AIDS event or death.		
DEATH:		
placebo	3TC	3TC+LVR
4.6%	2.4%	2.7%
22/482	22/935	13/475

There was a 53% reduction in mortality. There was no statistical difference between the 3TC arm and the 3TCLVR arm, but the study was not powered to detect it.