

National AIDS Treatment Advocacy Project
at the Human Retrovirus Conference
January 28-February 1, 1996, Washington, DC

PROTEASE INHIBITORS

Conference Highlights from days 3 & 4

It's Friday morning and I'm back in NY from what was an exhausting but exhilarating and exciting Conference. The promise of protease inhibitors and viral load utility provides us with the best case of optimism we've had to date. Of course, so far, the clinical endpoint data currently available to us, on protease inhibitors, is limited to the Abbott study described below. So, it remains to be seen how long the benefits from these drugs will last. However, the Merck data presented (see my earlier highlight article--[day 1](#)-- on this subject) is very encouraging regarding prolonged benefit. With the combination of Crixivan/AZT/3TC, 6/7 study participants (a small number, but soon we'll have data on additional individuals) still had undetectable viral load as far out as we yet have data (6 months). Additionally, it is encouraging to consider that with Crixivan monotherapy 40% of study participants remained undetectable at 48 weeks. Also presented at this conference is an accumulation of data indicating that viral load changes are predictive of disease progression and survival. This accumulation process is ongoing, as data submission to the FDA is also ongoing, for review and approval of Roche's application for expedited review of its RT-PCR test (viral load). An FDA hearing, to consider approval of this test, is scheduled for April 1.

Also, we still need to further explore how best to utilize these drugs. Further studies will need to be conducted, to examine protease inhibitor therapy for "early intervention" treatment--(determine when may be the best time to intervene in disease progression), sero-conversion treatment, the sequencing of the use of each different inhibitor--cross-resistance data will be crucial for this subject, the combination of 2 protease inhibitors, etc. I expect these studies will be conducted, but it is important to keep the pressure on the drug companies and the ACTG-NIH to quickly initiate this work and to do it comprehensively.

HIGHLIGHTS

(For more expanded details, NATAP's written report on protease inhibitors, with the very latest and most comprehensive data, will soon be available, both by mail and possibly from this site):

(1)--The data from the Abbott French study has been updated to 6 months. In this open-label drug combination, all participants received---ritonavir/AZT/ddC. Study entry criteria: CD4 50-250 or a drop of 200 to a level less than 350 over a recent 6 month period or 250-350 with symptoms, treatment naive, with 32 participants enrolled (11 discontinued during the study--2 for hepatic toxicity). All participants had an initial 2-week treatment with ritonavir and then AZT/ddC was added. The viral load reductions were as follows: 1.8 log at 4 weeks, 2.2 log at 8 weeks, 2.3 log at 16 weeks, 2.4 log at 20 weeks and 2.1 log at 24 weeks. At 5 months, approximately 40% of participants had undetectable viral load. This data from this study is based upon a small number of

individuals over a brief length of time (6 months, so far). It is important to consider this, in interpreting the data and applying the findings. The mean increases in CD4 are (baseline=160 CD4, n=32): 124 at 4 weeks (n=29), 125 at 8 weeks (n=27), 125 at 16 weeks (n=25), 143 at 20 weeks (n=20), 154 at 24 weeks (n=17). The mean CD4% (baseline=12%): 16% at week 4, 17% at week 16, 20% at week 20, 20% at week 24.

(2)--- Abbott's findings from a study of ritonavir, on Thursday morning, was met with excitement and was a well-attended late-breaker session (where Merck also presented their data for Crixivan/AZT/3TC). Study entry criteria: CD4 less than 101, at least 9 months previous drug treatment, concurrent treatment with up to but no more than 2 approved anti-retroviral drugs (3TC was excluded--was not approved at the start of this study), no active opportunistic infections (but you could have had prior OIs). Some of the concurrent antiviral therapies, that individuals were using included: AZT/d4T, AZT/ddI, ddC, ddI, d4T and AZT. The most widely used was monotherapy with AZT or d4T. Study participants were taking on average, 11 concomitant drugs while in study.

Although the study had 1,090 participants, for the sub-study examining viral load and CD4 changes, the n=159 and 215 respectively. The mean changes in viral load: 1.3 log at 2 weeks, 1.2 log at 4 weeks, 1.0 log at 8 weeks, .9 log at 12 weeks, .6 log at 16 weeks. The mean increase in CD4 (at baseline--mean CD4 about 28): 25 cells at 2 weeks, 40 cells at 4 weeks, 42 cells at 8 weeks, 40 cells at 12 weeks, 45 cells at 16 weeks. The mean increase in CD8 cells (baseline--mean CD8 about 475): 175 CD8 at 4 weeks, 300 CD8 at 8 weeks, 220 CD8 at 12 weeks, 200 at 16 weeks.

The very crucial data on PROGRESSION or DEATH: There was about a 42% reduction in death. For those individuals receiving ritonavir, the rate of death was 4.8% (n=543, 26 deaths). For the placebo group, the rate of death was 8.4% (n=547, 46 deaths). There was a 58% reduction in AIDS or death (this represents a combination of statistics for progression to AIDS and death)--for those taking ritonavir; there was a total of 85 such events for individuals taking ritonavir (out of an n=543)--15.7%; for those taking placebo--there was a total of 181 such events (for a total n=547)--33.1%.

The most common clinical endpoints were: death (as 1st event) 17--taking ritonavir, 27--taking placebo; esophageal candidiasis: 16--taking ritonavir, 38--taking placebo; CMV retinitis: 13--taking ritonavir, 17--taking placebo; PCP: 9--taking ritonavir, 16--taking placebo; CMV (other): 3--taking ritonavir, 13--taking placebo; wasting syndrome: 2--taking ritonavir, 8--taking placebo; lymphoma: 3--taking ritonavir, 6--taking placebo; Kaposi's Sarcoma: 8 taking ritonavir, 22--taking placebo. Important to remember, is the side effect profile of ritonavir: rises in triglycerides and cholesterol, rises in liver enzymes measurement--ALT & AST, rises in GGT. The dropout rate for those taking ritonavir was 15%, but only 7% in the placebo group.

Another consideration is the [list of drugs](#), issued by Abbott, that are NOT to be co-administered with ritonavir. This list consists of about 25 drugs, including Rifabutin. Please, adhere to these guidelines; consult your physician about which drugs you can and cannot take along with ritonavir. Oftentimes, there is a substitute that can be taken instead of the prohibited drug. The development of cross-resistance, to other protease inhibitors, from treatment with ritonavir, is also a concern.

COMMENTARY: When considering the viral load performance of this drug in this specific study, it is important to remember that the population being studied is very advanced: with the mean CD4 at baseline about 28. Being an advanced disease group, this could mean their virus population was more heterogenous than a group with significantly higher CD4 and lower viral load. Therefore, viral mutation can advance more efficiently than in a less advanced population. In the Crixivan/AZT/3TC study, where the early data looks good (see below), the study population was not as advanced in their stage of disease; the baseline CD4 was 142. In addition, in the Abbott study, there were compliance problems. Ritonavir was administered in a very distasteful liquid. Some study participants receiving ritonavir may not have taken the drug as they were supposed to, but told study coordinators that they were taking it according to instructions.

In the New England Journal of Medicine--Dec. 7, 1995, data was reported by Martin Markowitz et al, on an earlier Abbott trial. When a sensitive assay was used in a small subgroup of 20 patients (the total of participants enrolled were 62), they found viral load decreased by a mean of 1.7 log. At 12 weeks, it was at 1.1 log. The mean maximal decrease, reached at week 8, was 1.94 log. Although, this data is based on only 20 individuals, it brings into question the RNA results of the less than 101 CD4 study, presented at the Conference. But, it is uncertain how sustained this viral load response was, for this study discussed above from the New England Jnl. of Med. Also, the ritonavir administered for this 20-person sub-study was a capsule, not the liquid, which lends itself better to compliance. My point is, it is difficult to compare different studies. The side effect profile detected from this earlier study: liver enzymes, cholesterol, and triglycerides increased significantly during week 1. Elevations in cholesterol and triglycerides persisted through the 32 weeks of the study; there were increases from baseline of 30 to 40% for cholesterol and of 200 to 300% for triglycerides.

(3) Agouron was denied from presenting their data at the Conference, but a special meeting was convened across the street in a different hotel, where they presented their data. This drug is much earlier in its development stage than the other 3 inhibitors--saquinavir (already approved and available in the pharmacy), Abbott's ritonavir and Merck's Crixivan. We have not yet been notified of the emergence of any additional side effects.

They stated, in vitro data indicated a synergy of VIRACEPT with AZT, ddC, 3TC and additive benefit with AZT and 3TC. They presented their studies examining different dosing regimens. The data from protocol #510 was presented. At baseline there were only 40 participants. Study entry criteria: d4T naive, CD4 greater than 200, viral load greater than 15,000, AZT naive or experienced. The bDNA assay used measures RNA down to 500 copies; below that level of 500 is considered undetectable.

It is very important to remember, that the amount of information and data on this drug is more limited than available for the Merck and Abbott inhibitors; therefore, it's premature to judge the efficacy and safety of this drug on an evaluation of such few individuals over such a short period of time. The data available for this study extends only to 45 days. The study is still accruing, but, it appears, the mean CD4 at baseline is about 300 or slightly higher. The baseline RNA is between 50,00 to 70,000. There are 4 study arms: VIRACEPT 500 mg. 3x daily + d4T, VIRACEPT 750 mg. 3x daily + d4T, VIRACEPT

1000 mg. 3x daily + d4T, and d4T without VIRACEPT. At only 28 days, for about 24 evaluable participants, the CD4 increases for those receiving VIRACEPT/d4T ranged from about 100 to 200.

The viral load data is the same for each of the 3 different dose levels: the graph trended down to 2.5 log at 45 days. Remember, viral load at baseline was between 50,000 & 70,000; if your load was 49,000, a 2 log drop reduces your viral load to 490--below detectability. Agouron displayed a graph depicting the % of responders at 4 weeks for RNA (for a total of only 17 individuals); the data is the same for all 3 dose levels: greater than 1 log decrease--100%; greater than 1.5 log decrease--100% of participants; less than 500 copies, undetectable--75%. In a separate small VIRACEPT monotherapy study, where the baseline RNA was 50,000, the mean maximal log reduction was: 1.7 log--for the 500 mg. dose, 2.3 log--for the 750 mg. dose, 2.1 log--for the 1000 mg. dose. This is encouraging information. The side effect profile seems to compare reasonably well: most individuals taking VIRACEPT, have an increased amount of bowel movements per day and loose stools.

COMMENTARY: Remember, the data is limited; this data extends out only to 28 or 45 days which means we cannot judge whether these CD4 increases and viral load decreases will be maintained over time. In addition, the number of evaluable study participants is too small to be predictive. But, we can expect to learn much more about the performance of this drug from their upcoming large-scale trials. In contrast, Merck has studied 2,000 individuals using Crixivan; their recent Crixivan/AZT/3TC trial enrolled 97 patients, which is still considered small. Abbott's study described above, examining individuals with less than 100 CD4, enrolled 1,090 individuals, and the CD4 data is based on 159 individuals while the viral load data is based on 215. Agouron is conducting drug interaction studies. VIRACEPT is about to enter its large-scale pre-accelerated approval studies, which will enroll over 1,000 individuals for 6 different studies, and study two different doses--500 mg. 3x daily and 750 mg. 3x daily. Both AZT/3TC and d4T will be used in combination with VIRACEPT in these studies.

(4) On Thursday, Dr. Trip Gulick of NYU presented the Merck Crixivan data from the still ongoing trial examining the 3-drug combination of Crixivan/AZT/3TC. The mean baseline RNA was 39,800; the mean baseline CD4 was 142; the total number of enrolled participants at baseline was only 97. Bear in mind, that the results reported below are based on a small number of individuals. Throughout the months ahead, as the amount of data increases, updated reports will be available on the NATAP Web site home page.

The mean decreases in viral load for the 3-drug combination was: 1.8 log --at 4 weeks, 2.0 log--at 8 weeks, 2.3 log at 20 and 24 weeks. At 24 weeks, the data is based on only 7 evaluable study participants (but, soon we'll have data on 14 or more individuals); at 16 weeks, there were 20 to 24 evaluable participants. It is important to remember that the mean baseline RNA level is 39,800--so, a 2 log reduction is below the level of detectability (which is 500, in this case, by the Roche PCR kit); if there were a 3 log drop, you couldn't see it. The individuals who had a higher drop in viral load, had to have had higher levels at baseline, in order for it to be detected; a consideration of the baseline measure is important to the interpretation of viral load data. Therefore, the mean RNA drop should be 2 log at 24 weeks. The proportion of individuals with undetectable virus

are (baseline=39,800): 40% at 4 weeks, 80% at 8 weeks, 90% at 16 weeks, n=20 to 24), 86% at 24 weeks (6/7 participants); very soon we should have data on 14 individuals at 24 weeks. The mean increases in CD4 (baseline=142 CD4) are: 60 at 4 weeks, 75 at 8 weeks, 100 at 14 weeks, 100 at 20 weeks, 146 at 24 weeks.

For those taking Crixivan alone (monotherapy), the mean viral load reduction was: 1.7 log at 8 weeks, 1.4 log at 17 weeks, 1.3 log at 24 weeks. The proportion of individuals with undetectable virus is 44% at 24 weeks (4/9 individuals). The mean increase in CD4 is 100 at week 12 and 98 at 24 weeks. Merck's experience is that for some individuals, after viral load starts returning to baseline, the CD4 still remain elevated. The side effect profile: hyperbilirubinemia (raised bilirubin levels) occurs in 15% of those taking Crixivan; usually, the rise subsides; urolithiasis occurs at a rate of about 3%--one of the symptoms of this is the development of kidney stones. Some individuals developing this side effect, discontinued Crixivan treatment and then re-challenged successfully with the drug; others were able to continue taking Crixivan while the side effect was resolved. Rises in liver enzymes usually subside within weeks.

Merck's AZT/ddI/Crixivan study, #020:

These results were reported in January-1996 at the Human Retrovirus Conference. This is a 24 week study of treatment-naive individuals (less than 2 weeks AZT or ddI). There are 3 arms--26 per arm: Crixivan 600 mg. 4X /day, AZT/ddI--ddI 200 mg. 2x/day, Crixivan/AZT/ddI. The baseline viral load and CD4 were 102,000 copies and CD4 150. At week 24, the median viral load drop was 2.9 with the 3-drug combination; the median CD4 increase was 80-90 cells at 24 weeks. 60% of subjects on 3-drug therapy were below level of RNA detectability at 24 weeks (200 copies/ml of viral RNA). Merck reported that 60% of participants in both arms--Crixivan monotherapy and 3-drug combination--had at least a 50 CD4 increase, at 24 weeks. Merck said that due to compliance difficulties with taking ddI, there were 7/26 ddI discontinuations in the 3-drug arm and 3/26 in the AZT/ddI arm. Also, after 6 months, when unblinded, some individuals discontinued ddI. The side effects were as usual: 10-15% hyperbilirubinemia after 1 month therapy, it reversed without clinical symptoms; urolithiasis is expected to occur at a rate of about 2-3%.

COMMENTARY: Apparently, combining AZT/3TC with Crixivan is important to the sustained antiviral benefits. The consensus opinion is that multi-drug combination therapy, which includes a protease inhibitor, will delay the development of resistance, and therefore, prolong the benefits of therapy--rises in CD4 and decreases in viral load; and, hopefully prolong survival. But the development of cross-resistance, to other protease inhibitors, is a concern, from the use of Crixivan. Additionally, there are drug interaction concerns. For example, the concurrent use of rifampin is prohibited with Crixivan. There are additional drug interaction concerns; please, consult your physician about them.

Again, the amount of individuals studied in this trial is relatively small. The final results on all these participants have not yet been tabulated. Although this data is exciting, encouraging, and caused much optimism at the Conference, bear in mind that sometimes study results can change when examined in a much larger group of individuals. This study examines only the drug's effect on surrogate markers--CD4 and viral load. The

required "clinical endpoint" study--examining the drug's affect on progression to AIDS and survival-- is just now about to start. So, unlike the Abbott trial described above, which studies clinical endpoints, there is not yet data for those purposes for Crixivan. Of course, many individuals will not be able to wait for the data results of ACTG 320 (which is just beginning now), the study examining Crixivan for clinical endpoints--before having to make personal treatment decisions; additionally, in the near future other studies will be initiated exploring many different concepts. For those individuals who want to make a treatment decision, after the expected FDA approvals of ritonavir and Crixivan, consideration of this data will help in the decisions of which drug to use. NATAP's extensive written report will soon be available for all. It will review the data presented at our Jan. 6 forum at NYU (the videotaped event) and the data presented at this Conference.

One of the reasons, that some are being circumspect about these findings, is that AZT at first was shown to prolong life, but its benefits were limited. An important distinction is that viral load is a new measure, and AZT has minimal benefit to viral load, while protease inhibitors have a more profound effect. Multi-drug combinations, which include a protease inhibitor, have even a more profound effect on viral load and CD4. I remain cautiously optimistic.

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