National AIDS Treatment Advocacy Project

Late Breaker--Nevirapine Interaction Data with Indinavir Released November 20, 1996

below is a mixture of information from the manufacturer and the author's commentary

Today, Boehringer Ingelheim (BI) released their findings of an interaction study of nevirapine and indinavir to community advocates. Doctors and patients have been experimenting with this combination without the benefit of this data. The data is preliminary and does not predict the longer-term clinical outcome of combining these two drugs. It may be advisable to delay using the combination until more data is available, unless you have no other alternatives.

In January at the Human Retrovirus Conference, more data is expected to be presented that may be more helpful in deciding whether to combine nevirapine with indinavir. Previously released from BI, interaction data indicated a reduction of blood levels for saquinavir when used with nevirapine: a questionable combination. Data from the interaction study of nevirapine and ritonavir will not be available until the end of January 1997.

"Nevirapine is an inducer of hepatic cytochrome p450 metabolic enzymes predominantly of the 3A4 family. Thus, it has the potential to decrease the plasma levels of concomitantly administered drugs which utilize a similar metabolic pathway, such as protease inhibitors."

Currently,the FDA indication of approval for nevirapine is for its use with approved NRTIs, not with protease inhibitors. Eventually, BI expects to be able to apply to the FDA to ammend that indication, but presumably with more data than is currently available. Currently, use of this combination is not FDA approved, but is commonly referred to as "off-label" usage.

Study Protocol
24 HIV+ patients were enrolled; 19 are evaluable as 5 withdrew. Participants were permitted to continue other approved antiretroviral drugs they may have been taking, such as AZT,etc. Some were treatment-naive and some were not. The median baseline viral load was low--4,000 copies/ml (range undetectable to 286,000)-- and the lower limit of detection of viral load was 400 copies/ml.

Regimen--
Participants received indinavir (IDV) for 7 days at the currently recommended dose--800 mg every 8 hrs for. For the next 14 days, nevirapine (NVP) 200 mg once per day was added; For the next following 14 days, nevirapine at 200 mg twice per day was administered. This dose escalation method is standard for nevirapine.

Results--
"In the 19 evaluable patients, coadministration of IDV with NVP resulted in a reduction

in IDV plasma (blood) levels. The preliminary results indicate that co-administration of the two drugs resulted in a 28% mean reduction.....in IDV area-under-the-curve (AUC) values, an 11% reduction in IDV peak concentrations (Cmax) and a 38% reduction in IDV trough concentrations (Cmin)."

Commentary:
the overall blood levels of IDV were reduced by 28%; usually, soon after a drug is taken, the blood levels rise to a peak blood level (Cmax); that IDV peak is reduced by 11%, in this case. Near the end of the 8 hour period after taking indinavir, the blood levels lower to a trough before taking the next dose; it is expected after taking a drug that blood levels rise to a peak and then lower to a trough before taking the next dose; this trough blood level for IDV is reduced by 38%.

BI continues, "the range of AUC's at day 7 (which is the last day before adding NVP) was 5.44-34.57 ug hr/mL, and at day 36 (IDV+NVP) the range of AUC's was 6.62-26.30 ug hr/ml. Compared to historical controls, a nonsignificant reduction (less than 10%) in NVP AUC plasma (blood levels) concentrations was observed during combination with IDV".

Commentary:
BI characterizes the NVP blood level reduction of up to 10% as non-significant. Who knows what a 10% reduction really translates into as clinical effect. There can be variability between people in absorption of any drug. One individual can experience a 10% reduction in blood levels, while a 2nd individual may experience no change in blood levels. The range of AUC mentioned above indicates variability in blood levels experienced by study participants. But, BI said the inter-patient variability is less for this combination than that seen with NVP+saquinavir.

Viral Load Data--
After 96 days, 14/16 evaluable study participants were below the lower limit of detection (400 copies/ml) of the assay; the median baseline viral load was about 4,000. The viral load of 2/16 rebounded; BI would not to speculate as to why until further evaluation.

BI is continuing "to collect plasma samples to evaluate viral load since patients were invited to continue on the combination therapy in open-label follow-up.....to monitor virologic activity and drug plasma (blood) levels in order to obtain anecdotal data on the relationship between pharmacokinetics and antiviral response".

Commentary:
A viral load reduction from 4,000 to 400 is only a 1 log reduction; but, there was a wide range of baseline viral load values from 260,132 to under 400. Four individuals' baseline viral load were between 18-27,000; for them, to reach undetactable of 400, the reductions would range from 1.6-1.8 log. Generally, indinavir monotherapy can result in about a 2 log reduction. The two drugs should not be cross-resistant due to their different enzyme targets (reverse transcriptase and protease). It is difficult and premature to accurately assess the full potency of the combination and its durability.

Safety--

"In general, the combination of IDV+NVP has thus far been well-tolerated. Two patients discontinued due to rash attributed to NVP; the rashes were mild to moderate and resolved after discontinuation of study medication. The other 3 withdrawals were due to: kidney stone after 1 day on IDV (no prior history of kidney stone), protocol non-compliance and self-withdrawal.

The main safety concern for nevirapine is the potential for developing a rash. A composite percentage of rash development from the three studies presented at the FDA approval hearing: of those study patients on a nevirapine/nucleoside combination therapy, 37% developed a rash; of those in one of the nucleoside therapy treatment arms (without nevirapine), 20% developed a rash; grade 1 rash--20% in NVP arms vs 13% non-NVP arms; grade 2--10% in NVP arms vs 5% in non-NVP arms; grade 3--5.6% in NVP arms vs 0.8% in non-NVP arms; grade 4--2% in NVP arms vs 0.4% in non-NVP arms; patients permanently discontinued in the presence of a rash--6.7% in NVP arms vs 1.2% in non-NVP arms.

"There is a relationship between dosing and antiviral activity with both IDV and NVP. Increased resistance to IDV has been observed in studies where IDV was administered as monotherapy in doses less than 2.4 grams per day. It is not known how NVP in combination with IDV may contribute to the suppression of resistance to IDV. Likewise, the effect on the development of resistance to NVP when IDV is coadministered has not been established.

Dose modification--
"In this study, blood levels of IDV when coadministered with NVP were lower than levels of IDV when given alone. To adjust for this observed pharmacokinetic interaction, a dose increase of IDV to 1000 mg every 8 hours (3 times per day) should be considered when taking NVP 200 mg twice per day. This may result in an IDV plasma pharmacokinetic profile that closely resembles the 800 mg dose of IDV without NVP".

"Currently, there are not enough data to establish that the short or long term antiviral activity of IDV 1000 mg (every 8 hrs) with NVP 200 mg (2x/day) will differ from that of IDV 800 mg (every 8 hrs) with NVP 200 mg (2x/day). Thus the potential benefit of a dose increase of IDV must be evaluated with other issues (e.g. potential adverse effects, diminished compliance, and increased drug costs)."

Commentary:
The development of resistance to IDV, NVP or any other therapy is a possibility regardless of how compliant you may be. But, one could argue that if you are able to lower your viral load to a low enough level with a regimen (including this combination of NVP+IDV), then you may have adequately suppressed replication to prevent resistance to emerge for the drugs in the regimen. But, it is premature to presume too much. We have not studied this combination, of IDV+NVP, long enough to assess its durability. BI should test the study participants with the Ultra-sensitive Roche assay with the lower limit of detection of 20 copies. Incidentally, it is advisable to consider taking a nucleoside(s) along with this combination, if you decide to take it.

Prior to phase III studies. Merck was considering 1000 mg or 800 mg (every 8 hrs for

1000 or 800) as the dosing regimen with which they would proceed. They chose the 800 mg dose because they did not perceive a difference in efficacy but there appeared to be a higher potential incidence for a kidney stone at the higher dose. If you take a 1000 mg dose of IDV which is in turn lowered by 28% in its blood levels, can you assume the chance of a kidney stone is also lowered? we are not sure.

Again, data collection is ongoing; BI said, additional information will be presented at the Retrovirus Conference in January 1997; 96 days is normally too short a period of time upon which to base treatment decisions. But, individuals without viable alternatives initiated therapy with ritonavir/saquinavir with little information. After only 12-20 weeks, so far 3 dosing regimens appear relatively equal in efficacy, but one of them (600RTN+600SQV bid) had more incidence of liver enzyme elevations. If you have alternatives, it may be advisable to wait for more data.