National AIDS Treatment Advocacy Project

DMP-266: an NNRTI; early safety and efficacy data

This report combines data presented at the 4th Retroviruses & Opportunistic Infections Conference's Sunday Late Breaker session as well as additional information. January 27, 1997 from Jules Levin

---

Dr. Sharon Riddler, of the University of Pittsburgh, reported preliminary study results of this NNRTI (non-nucleoside reverse transcriptase inhibitor), which is in the same class of drugs as nevirapine and delavirdine.

This double-blind randomized study evaluates antiviral activity and tolerability of DMP-266 in combination with indinavir. Participants with CD4 between 100 to 500 and viral load above 20,000 received indinavir 800 mg every 8 hours for two weeks, and then the 30 patients enrolled were randomized in a 2 to 1 ratio to receive either DMP-266 + indinavir or placebo + indinavir for an additional 24 weeks.

21 participants were randomized to receive DMP-266 (200 mg once per day) with 800 mg indinavir (taken 3 times per day--i.e. every 8 hrs). 8 to 12 weeks into the study most patients increased their dose of indinavir to 1000 mg every 8 hrs because DMP-266 lowers blood levels of indinavir (indinavir AUC decreases 35%). The other 9 participants received indinavir monotherapy for the entire 26 weeks. Mean baseline CD4 and RNA in the DMP-266 indinavir arm were 164 and about 85,000 copies respectively. Mean baseline CD4 and RNA in the indinavir alone arm were 71 and about 131,800 copies respectively.

Results. After two weeks of indinavir monotherapy the mean reduction in plasma RNA was 1.25 log from baseline and the mean CD4 increase from baseline was 65 cells. After 26 weeks of study as measured by the test using 400 copies as the lower limit of detection of viral load, those taking indinavir monotherapy (n=9) had a mean reduction from baseline of about 1.5 log; participants (n=21) taking DMP-266+indinavir sustained a mean reduction of about 2.4 log. After 26 weeks of study when using a more sensitive test for viral load, those receiving indinavir monotherapy had a mean reduction in viral load of 2.2 log; and, those taking DMP-266+indinavir had a mean reduction in RNA of about 4 log.

Both treatment groups had mean increases in CD4 from baseline of about 100 cells after 26 weeks of study. 82% of those taking the combination were below the level of detection of assay (400 copies). 38% of those taking indinavir alone were below detection.

Safety. The investigator characterized DMP-266/indinavir treatment as generally well tolerated. One patient had grade 4 elevation in LFTs (liver function test); several cases of nephrolithiasis occurred but resolved; 8 patients taking combination had a rash, one discontinued due to rash; one person taking indinavir had a rash.

Other adverse events and their incidence for those taking combination were: headache-6, diarrhea-6, dry skin-5, pharyngitis-6, URI-5, sinusitis-5, depression-4, herpes simplex-4, and there were several additional ones. 5 patients discontinued from the combination treatment arm, 2 due to adverse events.

The above described data result from the use of 200 mg once per day dosing of DMP-266. Phase

II studies will explore 200, 400 and 600 mg once per day dosing regimens of DMP-266. In these studies three dosing regimens of indinavir will be explored--800 mg, 1000 mg and 1200 mg every 8 hrs. These regimens will be evaluated for safety, tolerability and efficacy. The combination of DMP-266 with AZT and 3TC will be explored. This combination could be an alternative to protease inhibitor therapy for those who may want to delay using a protease inhibitor. And indinavir+DMP-266 will be studied.

Commentary: It is important to learn more about cross-resistance between NNRTIs -- nevirapine, delavirdine and DMP-266. All 3 manufacturers should be forthright in sharing drug and isolates. In the past companies have not always cooperated in sharing this information. Companies should be held responsible for not being cooperative. In order for DuPont Merck to be prepared with cross-resistance data, Upjohn and Boerhinger Ingleheim will have to share information. The at-times bitter conflict between protease inhibitor manufacturers regarding the controversy of cross-resistance has been unpleasant and unsatisfactory. It might be helpful if the FDA would at least try to weigh-in with the NNRTI manufacturers on this subject. At the committee hearings for both delavirdine and nevirapine, the FDA did not attempt to assert any authority on this subject.

Research and treatment for HIV is headed towards minimizing the amount of times per day one must take medications. DMP-266 is taken once per day. The new Abbott protease inhibitor (ABT-378, report being prepared for this web site) too has potential for once per day dosing. Already a number of treatment regimens can be taken twice per day, and protease inhibitors that are currently recommended to be taken 3 times per day will be studied in 1997 in twice per day dosing regimens in combination with other protease inhibitors. Several protease inhibitors, when combined with specific other ones, produce higher and more sustained blood levels for each of the two or for one of the two. This may allow for protease-protease combinations in 2 times per day regimens. See 4th Retroviruses & Opportunistic Infections Conference Daily Highlight Reports on this web site for more detailed description of which protease inhibitors will be studied together.