National AIDS Treatment Advocacy Project

Combination use of Ritonavir and Saquinavir in HIV-infected patients--Preliminary Safety and Activity Data

Abstract # Th.B.934, authors- William Cameron, E Sun, M Markowitz, C Farthing, D McMahon, D Poretz, C Cohen, S Follansbee, D Ho, J Mellors, A Hsu, GF Granneman, R Maki, M Salgo, M Court, J Leonard

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For months, many have been waiting data on this combination, particularly AIDS treating doctors and people with AIDS, who have been anxiously anticipating some useful data. The negotiations between Roche and Abbott to conduct these studies began a year ago. The first trial in healthy HIV- volunteers began in December 1995, and the trial, under discussion here, in HIV+ individuals began in March 1996, and explores different dosing combinations of ritonavir and saquinavir.

The results discussed below are positive and promising, but it's important to note the results are preliminary, as these results consist of only 6 weeks of efficacy and safety data. We still are uncertain of what the optimal dosing regimen could be, the durability of these results and the longer-term safety of the combination.

Some of the concerns are:

- the data so far available and presented here for combination of ritonavir and saquinavir is based on only 63 study subjects; about 3,000 individuals were studied in clinical trials using saquinavir; the clinical trials of indinavir studied over 2,000 subjects; the trials of ritonavir studied over 1,500 individuals, and the trials for these 3 drugs took place over a period of about 2 years. This ongoing study of the combination of saquinavir and ritonavir began only several months ago. We do not yet know the longer-term safety profile for this combination. Ritonavir raises saquinavir's blood levels much higher than those resulting both from the currently recommended dosing regimen of saquinavir and from the blood levels of the new more potent formulation of saquinavir, which is now in clinical trials.

- although, as you will see the data below, after 6 weeks the CD4 and viral load improvements are impressive, we don't yet know how durable they will be; still,

    - Dr. Cameron, a study investigator, said--".....Animal and human pharmacokinetics studies have demonstrated that the co-administration of ritonavir and saquinavir achieves high and sustained plasma levels of both drugs, and thus should maintain prolonged vital suppression, reducing the opportunity for the emergence of viral resistance".

- the data presented below is for 2 of the 4 dosing regimens being studied in this trial; there is not yet data available for the other two regimens. Which one of the 4

regimens will prove to be most effective remains a question. Of course, it is possible that all may be fairly equally effective. However, for those individuals with few if any remaining treatment options, using the combination of ritonavir and saquinavir represents an important treatment option. These individuals can take two drugs that they've never taken before. This represents a particularly significant opportunity, which many have already chosen to seize.

At the Vancouver AIDS Conference, the Dr. William Cameron, of Canada's Ottawa General Hospital, presented the study results.

--He said,

- "these are the only two protease inhibitors to show improvement in survival and disease progression".

  Commentary--I think that Crixivan will display the benefits to survival and disease progression at least as well as these two drugs.

- "ritonavir enhances and sustains saquinavir blood levels".

  Commentary--the important premise underlying the combination of these two drugs is that ritonavir suppresses a mechanism of liver metabolism which allows other drugs to have a higher blood level. High blood levels of saquinavir result from using ritonavir together with Saquinavir.

- "these two drugs have divergent resistance patterns".

  Commentary--Apparently, the mutation profile that causes saquinavir resistance does not significantly overlap with the mutation profile of ritonavir. The most relevant in vivo mutations for ritonavir occur at 36, 54, 71, 82, 20, 46, 84--respectively; for saquinavir 48 and 90 are the most relevant locations for mutation, and thereby resistance.

Cameron presented a slide displaying the:

- Effects of ritonavir on saquinavir blood levels (single dose)"

It depicted the effect of different regimens and dosing on saquinavir AUC (ug. hr/ml):

- 200 mg of saquinavir monotherapy did not cause a detectable AUC;
- 400 mg caused a barely detectable AUC level of saquinavir;
- 600 mg was not much of an improvement , all 3 with a measurement
- under 1;
- 200 mg saquinavir combined with 600 mg ritonavir had a measurement of about 12;
- 400 mg saquinavircombined with 600 mg ritonavir had a measurement of about

25;

- 600 mg saquinavircombined with 600 mg ritonavir had a measurement of about 40.

Cameron presented a slide entitled:

- Ritonavir enhances Saquinavir (blood) levels in human studies at two weeks"

It showed the median steady-state AUC (ug.hr/ml)--

- a saquinavir dose of 600 mg monotherapy every 4 hours, for a daily total
- of 3,600 mg, the measure was about 2;
- a saquinavir dose of 1,200 mg monotherapy every 4 hours, for a total daily dose of 7,200 mg, the measure was about 10;
- saquinavir 400 mg every 12 hours combined with 400 mg ritonavir every 12 hours resulted in an AUC measure of about 30;
- saquinavir 600 mg every 12 hours combined with ritonavir 600 mg every 12 hours (daily dose of 1,200 mg saquinavir) resulted in an AUC measure of about 60.

Commentary--As you can see, ritonavir greatly increases blood levels of saquinavir. Again, we do not yet know the longer-term effects of raising saquinavir blood levels to such high levels--durability and safety.

THE STUDY:
The study objectives are to evaluate dose combinations, pharmacokinetics, virology and long-term safety, tolerance and activity.

120 HIV-infected individuals, with 100-500 CD4 cells/mm3, were randomized in a multi-center study with all subjects receiving open-label saquinavir and ritonavir. All participants discontinued use of RT inhibitors for the study. Drugs were initiated in escalating dose fashion through the first few days to optimize tolerability.

After a 2-week safety evaluation period, study subjects are randomized to four groups:

- ritonavir 400 mg bid + saquinavir 400 mg bid (n=30)
- ritonavir 600 mg bid + saquinavir 400 mg bid (n=30)
- ritonavir 400 mg tid + saquinavir 400 mg tid (n=30)
- ritonavir 600 mg bid + saquinavir 600 mg bid (n=30)

Baseline HIV RNA and CD4:

HIV RNA (log10 copies/ml)	ritonavir 400 mg bid saquinavir 400 mg bid (n=33)	ritonavir 600 mg bid saquinavir 400 mg bid (n=30)
mean	4.53 (33,884 copies/ml)	4.68 (47,863 copies/ml)
median	4.63 (42,658 copies/ml)	4.65 (44,668 copies/ml)

CD4 T-lymphocytes/mm3	RTV 400mg bid+ SQV 400mg bid (n=33)	RTV 600mg bid+ SQV 400mg bid (n=30)
mean	274	299
median	249	255

HIV RNA and CD4, CD8 changes--

(n=61 at baseline, 59 at 2 weeks, 58 at 4 weeks, and 42 at 6 weeks--this is the total number of individuals upon which the data is based inclusive of both dosing groups).

400mg RTV bid + 400 mg SQV bid--

- at 2 weeks RNA reduction & CD4 increase from baseline approx.-- 1.6 log - 25 cells
- at 4 weeks RNA reduction & CD4 increase from baseline approx.-- 2.1 log - 50 cells
- at 6 weeks RNA reduction & CD4 increase from baseline approx.-- 2.2 log - 80 cells

600 mg RTV bid + 400 mg SQV bid--

- 2 weeks--viral load reduction & CD4 increase from baseline approx.-- 1.6 log - 70 cells
- 4 weeks--viral load reduction & CD4 increase from baseline approx.-- 2.2 log - 85 cells
- 6 weeks--viral load reduction & CD4 increase from baseline approx.-- 2.6 log - 100 cells

Commentary:
The number of study participants for which this data applies is small, and the resulting differences in data between the two groups is small, so at most you may be able to say there is a suggestion of a trend that the 600mg RTV+400mg SQV 400 mg is superior to the 400mg RTV bid/400mg SQV bid group; but, you could just as easily say the differences in data between the 2 groups is too small to draw any conclusion. It is also important to remember that the 2 other dosing regimens, for which we don't yet have

efficacy data, are being studied (600mg bid RTV/600 mg SQV bid and 400mg RTV tid/400mg SQV tid), and they could prove to be superior (in terms of safety and/or efficacy) to both of the groups discussed here. *end of commentary*

Reduction of viral load below 200 copies/ml at 6 weeks--47% had undetectable RNA in the 400mg RTN bid/400mg SQV bid group, 65% were undetectable (below 200 copies/ml) in the group receiving 600 RTN bid/400 SQV bid.

at 6 weeks----70% in the 400/400 bid group had either a 2 log decrease in RNA from baseline or were below 200 copies (undetectable).

--86% in the 600 RTV/400 SQV group had either a 2 log decrease in RNA from baseline or were below the level of detection for this test (200 copies/ml).

Commentary:
Again, this is a small data set, but the graph line depicting the % of individuals who were RNA undetectable appeared to be ascending.*(end of commentary)*

CD8 changes:

- at 6 weeks--the increase in CD8 from baseline is 175 in the 600 RTV/400 SQV group
- at 6 weeks--the increase in CD8 from baseline is 100 in the 400 RTV/400 SQV group

Tolerance and safety of Ritonavir + Saquinavir

	RTV 400mg bid + SQV 400mg bid (n=33)	RTV 600mg bid + SQV 400mg bid (n=32)
Adverse symptoms--		
--Circumoral paresthesia (tingling around mouth)	25	27
--Diarrhea	21	24
--Fatigue	14	14
--Nausea	12	12
--Flushing	7	17
Lab abnormalities (grade 3 or 4)--		
--ALT increase (liver function test)	1	2
--Triglyceride increase	2	5
--Uric acid increase	1	0
--Glucose increase	1	0
--CPK increase	1	1

Discontinuations	1	1

NOTE-- The rate of discontinuation in this study, as well as in other studies, may be lower than the rate of discontinuation with ritonavir as it is used in private practice. This could be due to the management of side effects by the treating physician. The nurse and doctor running this study are very adept with properly informing individuals, who are taking ritonavir, on what side effects to expect, how to deal with them, how to properly use the dose escalation method recommended by Abbott, and generally guiding individuals through the process of acclimating to taking ritonavir. But, in private practice the treating physician may not be as well informed informed about the proper use of rironavir; and/or, they may not take the time to acclimate their patients in the details of properly using the drug.

Future directions for studies as outlined by Abbott--
ritonavir+saquinavir in combination with:

- AZT+3TC
- d4T+ddI
- d4T+3TC

RTV+SQV+RT inhibitor(s):

- newly infected individuals
- advanced disease
- HIV transmission and prevention
- remission induction

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