National AIDS Treatment Advocacy Project

Ritonavir + Saquinavir: 24 week data

Our initial report containing the efficacy data (CD4 and blood plasma viral load) on ritonavir+saquinavir from the conference is in our newsletter--NATAP Reports -- available on this web site or by mail in a printed form. This is a supplement to that report and taken together the two reports are intended to be a more thorough discussion of data.

This open-label pilot study of the first protease-protease combination to be explored in a trial started with 141 participants and randomized individuals to 1 of 4 groups each with a different dose regimen:

- Group A- 400 mg ritonavir bid (every 12 hrs) + 400 mg saquinavir bid (every 12 hrs)
- Group B- 600 mg ritonavir bid (every 12 hrs) + 400 mg saquinavir bid (every 12 hrs)
- Group C- 400 mg ritonavir tid (every 8 hrs) + 400 mg saquinavir tid (every 8 hrs)
- Group D- 600 mg ritonavir bid (every 12 hrs) + 600 mg saquinavir bid (every 12 hrs)

At this conference, Dr. John Mellors, of the University of Pittsburgh, reported 24 weeks data for Groups A & B, and 20 weeks data for Groups C & D.

Safety and Tolerability				
	A 24 wks	B 24 wks	C 20 wks	D 20 wks
RTV dose(mg) **SQV dose(mg)**	400 bid 400 bid	600 bid 400 bid	400 tid 400 tid	600 bid 600 bid
ADE-(Adverse Drug Event) at least moderate and possibly related Circumoral parasthesia Diarrhea Asthenia Nausea Taste perversion Peripheral parasthesia	 1 4 1 5 1 1	 3 9 3 7 0 4	 1 5 8 4 3 0	 3 11 10 8 3 1

Lab event (grade 3 or 4) SGOT (AST) increase SGPT (ALT) increase GGT increase Triglycerides	2* 2* 3 6	1 2 3 9	1 1 1 9	7 7 5 11
Discontinuation due to ADE	1	5	8	3
*includes one patient that dose escalated to 600 mg bid RTV				

Circumoral parasthesia can be a tingling around the facial area; peripheral parasthesia may consist of similar feelings in feet or hands; asthenia is a malaise or fatigue.

The side effects are more pronounced in Groups C & D. The tid regimen (Group C) is not recommended, as study participants are switching to a bid regimen (note the discontinuation rate). The dose regimen of Group D has the most pronounced side effects (compare the incidence of diarrhea, asthenia, nausea, LFT elevations, etc.).

Commentary: The efficacy data is available in our newsletter "NATAP Reports". At 6 months the two dosing regimens, Groups A & B, indicate equal improvements in CD4 and viral load; and, because of the side effect profile it appears as though Groups C & D are not preferable choices. An important question is whether Group A or Group B is the preferable dosing regimen. Group A is taking 50% less ritonavir than Group B, and the side effect profile is more favorable. If tolerance is an issue, the 400/400 (Group A) dose may be preferred. But, the 600/400 (Group B) dosing regimen has certain pharmacokinetics characteristics you may want to consider: because you are taking 50% more ritonavir, the peak, trough and AUC blood levels for both ritonavir and saquinavir are higher. Is that an advantage? In the light of the fact that after six months both groups show equal efficacy, it may not be a factor. If you were taking ritonavir without saquinavir, 400 mg of ritonavir would be sub-optimal and cause resistance.

Transaminase Elevations on Ritonavir-Saquinavir Therapy
Elevations of LFTs (liver function tests)

	patients with grade 3/4 SGPT (ALT)	Total patients
All patients	12	141
By treatment assignment: RTV 400 bid+SQV 400 bid RTV 600 bid+SQV 400 bid RTV 400 tid+SQV 400 tid RTV 600 bid+SQV 600 bid	 2* 2 1 7	 35 36 33 37

By baseline liver status: - Normal baseline SGPT and Hep B Ag negative & Hep C Antibody negative	2 7	85 41
- Abnormal baseline SGPT	4	7
- Hep B Ag positive	4	10
- Hep C Ab positive		
*One patient dose escalated to 600 mg bid RTV; other patient had acute hepatitis A		

Dr. Mellors recommended that the 600 mg/600 mg dose should not be used for those with Hepatitis B or Hepatitis C co-infection.

Commentary: Participants who were positive for the Hepatitis B Antigen or the Hepatitis C Antibody, prior to starting study medications, were most likely to experience grade 3/4 elevations of LFTs. As is usual with study protocols, participants who experience such elevations in blood lab values are withdrawn from the study. Individuals who experience such elevations in LFTs outside of study restrictions, who are given the opportunity of some time to work through the problem, may experience a decline in their LFTs, and their LFTs may over time decline to or towards their baseline LFT values. Some individuals given this opportunity to work through the LFT elevations are not responsive with declines and may have to stop the medications. In any event, it is important to closely monitor LFT values after starting therapy with ritonavir+saquinavir.

It is thought that the available protease inhibitors--saquinavir, indinavir, ritonavir, nelfinavir--do not adequately penetrate the CNS. It is suggested that at least one drug (and if possible two may be preferable) that penetrates the CNS be included in a multi-drug combination therapy. It appears as though AZT, d4T and nevirapine may penetrate the CNS adequately enough. There is some clinical data supporting the benefit of AZT, but additional studies are needed to address this application of d4T, nevirapine, and AZT.

Correlation of Compliance (or adherence) with Treatment Response (viral load below 200 copies/ml at week 24) in this ritonavir/saquinavir study.

Study investigators examined the role of compliance in achieving certain treatment goals as measured by viral load values (rendering viral load below 200 or 1,000 copies).

- Compliance was assessed by pill counting at study visits
- non-compliant patients were defined as:

  -below 86% medication compliance at doses of 400 mg bid

  -below 63% medication compliance at doses of 600 mg bid

- 54 of the 71 patients in Groups A & B were included
- 17 were excluded for:

  -non-subtype B (2)

  -discontinuation before week 24 (8)

  -RTI added before week 24 (4)

  -incomplete study records (3)

The investigators concluded that compliance is highly correlated with treatment response:

	Week 24 viral load	
compliant patients	below 200 90%	below 1,000 97%
non-compliant patients	66%	73%
p-value*	0.096	0.018
*Fischer's exact test		

Commentary: Of course there are other factors involved in being able to achieve full suppression, but the implications are clear how important compliance/adherence can be to successful treatment.

NATAP has published a compliance manual called "Protease Inhibitor Users Guide, How to Maximize the Benefit Of Protease Inhibitors". It discusses the compliance concerns of taking each of the approved protease inhibitors--hydration, eating, drug interactions, side effects, storage, viral load monitoring, etc. It lays out the compliance differences between each of the inhibitors. A number of clinics, ACTU sites, private practitioners, and individuals have ordered copies and find it a useful educational tool. We have distributed over 7,000 copies so far and have depleted our inventory. However we are now printing additional copies. Please contact NATAP if you would like the pamphlet for yourself or your organization's staff or clients.

The investigators showed some data indicating that viral load after 12 weeks of therapy with ritonavir/saquinavir in this study is predictive of treatment response at week 24.

viral load at week 12	viral load below 200 at wk 24	p-value*

below 1,001	98%	below 0.005
above 1,000	25%	
below 201	93%	below 0.036
above 200	66%	
*Fischer's exact test		

Commentary: It appears to me that the data from this table immediately above indicates that if taking ritonavir/saquinavir, and after 12 weeks if your viral load is not below 200 (but your goal is to be below 200) then you may want to consider adding other drug(s). In fact, when initiating therapy with ritonavir/saquinavir, you may want to consider adding another drug(s) at the start or soon after. It appears as though there are advantages to using drugs from different classes: protease inhibitors, nucleosides, non-nucleosides. It is suggested that it is advantageous to include at least one drug that penetrates the CNS. Four drug regimens are beginning to be the subject of clinical studies; a study of ritonavir/saquinavir/AZT/3TC has started.

In this ritonavir/saquinavir study, 7/71 participants added 2 RTIs to ritonavir/saquinavir for failure to achieve or maintain viral load below 200 copies/ml. They all added d4T/3TC seemingly coincidentally (possibly because they had extensive prior AZT experience). Six out of 7 of these participants' viral load fell to below 200 copies and remain below 200 for a follow-up period of 4-16 weeks so far.