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Saquinavir/Low-dose Ritonavir: its use in HIV Infection

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Abstract

Exposure to saquinavir can be increased considerably by pharmacokinetic enhancement with ritonavir, without having a substantial impact on tolerability. Clinical trials indicate that both once-daily and twice-daily saquinavir/ritonavir treatment regimens, generally at dosages of 1,600 mg/100 mg once daily and 1,000 mg/100 mg twice daily, provide potent and sustained viral suppression and are well tolerated. In addition, data suggest that "double-boosting" strategies, including the combination of saquinavir with lopinavir/ritonavir, provide valuable treatment options in the salvage setting.

Key words

Pharmacokinetics. Ritonavir. Saquinavir. HIV infection. Boosted.

Pharmacokinetics of saquinavir boosting

Pharmacokinetic enhancement or 'boosting' has gained momentum and is increasingly being used in clinical practice. Boosting of saquinavir is usually achieved by the administration of low-dose ritonavir[1-3], which should be given simultaneously in order to maximally increase saquinavir exposure[4]. Importantly, exposure to saquinavir can be increased considerably without having a substantial impact on saquinavir-related tolerability, as no upper limit to the therapeutic window of saquinavir has been identified to date[1]. However, since the toxicity of ritonavir is directly proportional to its plasma levels[1,5-7], administration of lower (100-200 mg) ritonavir doses diminishes the potential for ritonavir-associated adverse effects such as nausea, vomiting, oral paraesthesia, taste perversion and elevated lipid levels[1,5-7].

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The use of low-dose ritonavir to improve the tolerability profile of boosted saquinavir does not, however, diminish the boosting effect of ritonavir on saquinavir: a combined pharmacokinetic analysis of two dose-ranging studies indicates that the boosting effect of ritonavir on saquinavir is similar over the dose range 100-400 mg twice daily (BID)[2]. In addition, in HIV-1 infected individuals, the combination of saquinavir/ritonavir 1,000 mg/100 mg BID resulted in higher exposures to saquinavir compared with the exposure to saquinavir seen historically using the saquinavir/ritonavir 400 mg/400 mg BID combination[8] (Fig. 1).

The doses of saquinavir and ritonavir usually employed in clinical investigations of boosting strategies are presented in table 1.

Addition of ritonavir leads to significant increases in saquinavir exposure irrespective of whether the hard gelatin capsule (HGC) (Invirase®) or soft gelatin capsule (SGC) (Fortovase®) formulation is used[3,9-12]. In fact, an improvement in ritonavir-boosted saquinavir plasma levels with the HGC compared with the SGC formulation has been seen in comparative studies using saquinavir/ritonavir 1,000 mg/100 mg BID in healthy subjects and saquinavir/ritonavir 1,600 mg/100 mg once daily in HIV-1 infected patients[12-13]. This is of relevance because the SGC formulation contains the excipient capmul,

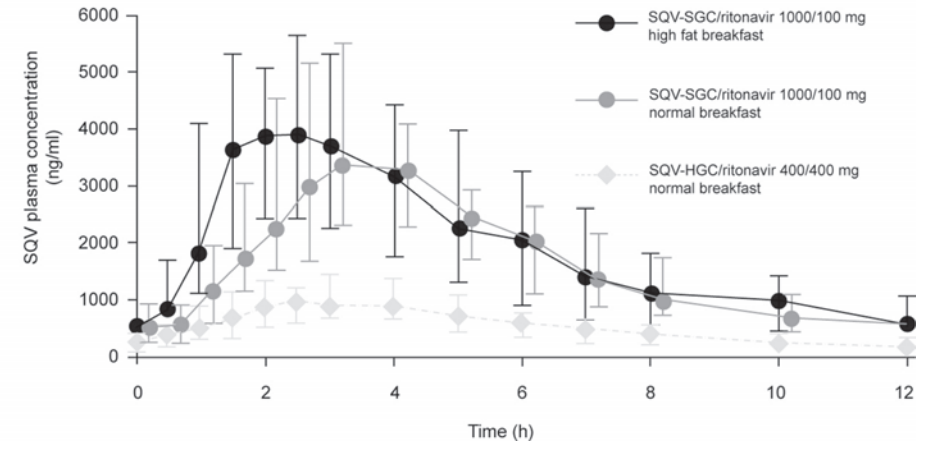

Figure 1. *Saquinavir/ritonavir 1,000 mg/100 mg BID achieves higher saquinavir plasma levels than saquinavir/ritonavir 400 mg/400 mg BID in HIV-1 infected subjects.*
Adapted with permission from Lippincott Williams & Wilkins. Veldkamp, et al. Steady-state pharmacokinetics of twice-daily dosing of saquinavir plus ritonavir in HIV-1-infected individuals. J Aquir Immune Defic Syndr 2001;27(4):344-9[8].

Table 1. *Doses of saquinavir and ritonavir usually employed in clinical investigations of boosting strategies*

Dosage schedule	**Saquinavir/ritonavir dose**
Twice daily (BID)	1,000 mg/100 mg
Once daily	1,600 mg/100 mg
Double boosting (BID)	1,000 mg/100 mg plus lopinavir 400 mg

which may be responsible for some of the gastrointestinal adverse events seen with this formulation[14]. This excipient is absent in the HGC formulation, thus providing a formulation which, when boosted with ritonavir, has an improved tolerability profile without loss of saquinavir exposure[12]. This may be beneficial to many patients who are unable to tolerate the gastrointestinal side effects associated with the SGC formulation, or in whom the large size of the soft gelatin capsules or their need for refrigeration is a problem.

Clinical studies of boosted saquinavir

A number of clinical trials have now evaluated saquinavir/ritonavir treatment regimens, at the dosages of 1,600 mg/100 mg once daily and 1,000 mg/100 mg BID. Also under investigation is the double-boosted regimen of saquinavir 1,000 mg plus lopinavir/ritonavir 400 mg/100 mg BID.

Twice-daily boosted protease inhibitor treatment

To date, clinical data on the efficacy and safety of the boosted saquinavir/ritonavir 1,000 mg/100 mg BID regimen are available from three main studies (Table 2).

MaxCmin I is the first head-to-head comparison of ritonavir-boosted protease inhibitor (PI) therapies. This multicentre trial compares a saquinavir/ritonavir 1,000 mg/100 mg BID treatment regimen with indinavir/ritonavir 800 mg/100 mg BID, both in combination with two nucleoside reverse transcriptase inhibitors (NRTI) in antiretroviral-*naïve* and -experienced patients (Table 2). In a prospectively planned interim analysis including data from 306 patients, 68 and 53% of patients in the saquinavir/ritonavir and indinavir/ritonavir group, respectively, had effective viral load suppression (< 400 copies/ml) after 48 weeks of therapy (intention-to-treat [ITT], switch or discontinuation = failure)[15]. Furthermore, at week 48 the proportion of patients remaining on randomised treatment with HIV RNA values < 400 copies/ml was 93 versus 90% respectively (on treatment [OT] analysis)[15].

The improved efficacy with the BID boosted regimen of saquinavir/ritonavir when compared to indinavir/ritonavir in the MaxCmin I trial was related to a better tolerability profile of saquinavir/ritonavir. At 48 weeks, 62 patients had at least one grade 3 or grade 4 adverse event in the indinavir/ritonavir group compared with 30 patients in the saquinavir/ritonavir 1,000 mg/100 mg BID group ($p = 0.0004$)[15]. In particular, there was a higher incidence of grade 3 or 4 renal, nervous system, pulmonary and dermatological adverse events in the indinavir/ritonavir group compared with the saquinavir/ritonavir group. Furthermore, 28% of patients in the indinavir/ritonavir group withdrew from the study due to adverse events compared with only 15% of patients receiving the saquinavir/ritonavir boosted regimen[15]. The majority of the grade 3 or 4 adverse events in the saquinavir/ritonavir group were gastrointestinal in nature. Use of the HGC formulation of saquinavir in combination with ritonavir in this situation may lead to a reduction in these adverse events while providing similar saquinavir plasma

Table 2. *Clinical efficacy data available on boosted saquinavir/ritonavir regimens (includes all available data at time of publication)*[10,13,15-23]

Reference	Study design	Treatment regimen	Patient numbers and characteristics	Median baseline HIV RNA level (log_{10} copies/ml) and CD4+ cell count (cells/μl)	Main efficacy results
Twice-daily therapy					
Cahn, et al., 2002	Prospective, open label, parallel group, randomized, multicentre	SQV/RTV 1,000/100 mg BID plus two NRTIs BID	ARV-*naïve* or ARV-experienced (n = 306)	RNA = 4.0 CD4+ = 272	**48 weeks ITT** HIV-RNA < 400 copies/ml: 68%
		IDV/RTV 800 mg/100 mg BID plus two NRTIs BID		RNA = 4.0 CD4+ = 280	**48 weeks ITT** HIV-RNA < 400 copies/ml: 53%
Valer, et al., 2002	Prospective, multicentre	SQV/RTV 1,000/100 mg BID plus two NRTIs BID	PI-experienced (n = 102)	Mean RNA = 5.0 Mean CD4+ = 367	**24 weeks** HIV-RNA < 50 copies/ml: 60%
Piketty, et al., 1999; 2000; 2001	Prospective, open label, single arm	SQV/RTV 1,000/100 mg BID plus EFV 600 mg once daily plus two NRTIs BID	SQV and EFV-*naïve* PI-experienced (n = 32)	RNA = 4.31 CD4+ = 258	**24 weeks ITT** HIV-RNA < 500 copies/ml: 71% HIV-RNA < 50 copies/ml: 45% **48 weeks ITT** HIV-RNA < 500 copies/ml: 61% HIV-RNA < 50 copies/ml: 58%
Once-daily therapy					
Montaner, et al., 2001	Prospective, open-label, randomized, multicentre	SQV/RTV 1,600 mg/100 mg once daily plus two NRTIs BID	ARV *naïve* (n = 159)	RNA = 4.78 CD4+ = 372	**24 weeks** HIV-RNA < 400 copies/ml: 70% (ITT); 97% (OT)
		EFV 600 mg once-daily plus two NRTIs BID		RNA = 4.72 CD4+ = 341	**24 weeks** HIV-RNA < 400 copies/ml: 82% (ITT); 94% (OT)
Cardiello, et al., 2002 Cardiello, et al., 2002 [abstract]	Prospective, open-label, single arm	SQV/RTV 1,600 mg/100 mg once daily plus two NRTIs BID	ARV-experienced (n = 69)	RNA = 4.7 CD4+ = 356	**24 weeks** HIV-RNA < 50 copies/ml: 93% **48 weeks** HIV-RNA < 50 copies/ml: 91%
López-Cortés, et al., 2002	Prospective, open-label, single arm, single centre	SQV/RTV 1,200 mg/100 mg plus EFV 600 mg once daily	ARV-experienced (n = 42)	Mean RNA <50–696,000 CD4+ = 565	**52 weeks** HIV-RNA < 50 copies/ml: 71.4%
Peytavin, et al., 2001	Prospective, open-label, single arm, multicentre	SQV/RTV 1,600 mg/100 mg once daily plus two NRTIs	PI-*naïve* (n = 18); PI-experienced (n = 17)	PI-*naïve*: RNA = 4.97 CD4+ = 219	**PI *naïve*, 12 weeks** HIV-RNA dropped to 2.70 log_{10} copies/ml
				PI-experienced: RNA = 2.3 CD4+ = 601	**PI experienced, 12 weeks** HIV-RNA < 200 copies/ml: 64%
Mallolas, et al., 2001	Prospective, open-label, single arm	SQV/RTV 1,600 mg/200 mg once daily plus two NRTIs	ARV-experienced (n = 18)	RNA = 3.5 CD4+ = 479	**12 weeks** HIV-RNA < 200 copies/ml: 85%

SQV = saquinavir
RTV = ritonavir
IDV = indinavir
EFV = efavirenz
NRTI = nucleoside reverse transcriptase inhibitor
ITT = intention-to-treat analysis
OT = on-treatment analysis
ARV = antiretroviral

concentrations, as indicated by a pharmacokinetic study in healthy volunteers[12].

The MaxCmin 2 study is the next head-to-head comparison of ritonavir-boosted PI therapy. Enrolment into this ongoing clinical trial, which is comparing saquinavir/ritonavir 1,000 mg/100 mg with lopinavir/ritonavir 400 mg/100 mg, both taken once daily with two NRTIs, was completed in January 2002, with the first data anticipated at the end of 2002.

The response to a saquinavir/ritonavir 1,000 mg/100 mg BID-based regimen in 144 heavily PI pretreated patients was evaluated as part of a Spanish multicentre, prospective trial[16]. There were a total of 42 withdrawals, few of which were due to tolerability problems or virological failure (these were each responsible for 5 withdrawals). Data from 102 patients who had completed 6 months' therapy have been presented (Table 2). Following 6 months of therapy, 76.6% of patients had a significant virological response (defined as > 1 $\log_{10}$ drop and/or a HIV-RNA titre < 50 copies/ml) and 60% of patients had HIV-RNA < 50 copies/ml. In a subanalysis involving 51 patients, the response to therapy was found to differ significantly depending on the presence of PI mutations associated with a loss of susceptibility to saquinavir. A better virological response (defined as above) was seen in subjects with < 4 saquinavir mutations (a response was observed in 89 and 57% of patients with < 4 or > 4 saquinavir mutations, respectively, $p < 0.05$)[16].

A saquinavir-HGC/ritonavir 1,000 mg/100 mg BID combination has been successfully employed in a study assessing the safety and efficacy of a five-drug regimen including efavirenz in patients who failed conventional triple drug regimens including indinavir or ritonavir (Table 2)[10,17]. Forty-eight weeks after switching to the five-drug regimen, 61% of patients had HIV-RNA < 500 copies/ml and 58% had HIV-RNA < 50 copies/ml. In this study, phenotypic resistance to saquinavir, defined as a >10-fold reduction in susceptibility, was found to be predictive of outcome (Fig. 2). Despite this, 25% of patients with phenotypic resistance were found to have a viral load of < 50 copies/ml after 24 weeks, as did 58% of sensitive patients. After a 48-week follow-up, the proportion of patients with a viral load of < 50 copies/ml had increased to 33% in the baseline-resistant group and 74% in the susceptible group[17].

Cross-study comparisons suggest that the efficacy results of the above study compare favourably with those of a similar study with lopinavir/ritonavir (400 mg/100 mg or 533 mg/133 mg BID) in which efavirenz was also administered[24]. However, in the saquinavir/ritonavir 1,000 mg/100 mg BID study no significant increases in serum cholesterol or glucose levels were observed, although a mild increase in serum triglycerides occurred and no grade 3/4 laboratory toxicities were reported[18]. However, in the study involving lopinavir/ritonavir, grade 3/4 laboratory abnormalities in total cholesterol (> 300 mg/dl or > 7.8 mmol/l) and triglycerides (> 750 mg/dl or 8.4 mmol/l) were seen in 9 and 9.3% of patients, respectively[25].

Furthermore, in 23 patients who switched from a saquinavir/ritonavir 400 mg/400 mg to saquinavir/ritonavir 1,000 mg/100 mg as part of a four-drug BID regimen, reductions in triglyceride and cholesterol levels were reported following the switch[26]. After 6 months, fasting triglyceride levels fell from 7.1 to 4.2 mmol/l ($p = 0.038$) and cholesterol levels fell from 8.3 to 6.1 mmol/l ($p > 0.05$). The improved tolerability was accompanied by continued suppression of viral replication (< 400 copies/ml)[26].

Once-daily boosted protease inhibitor treatment regimen

There is a range of clinical data to support the boosted saquinavir/ritonavir BID 1,000 mg/100 mg regimen as a valuable boosted PI treatment option in HIV-infected patients. Once-daily therapy is an attractive treatment option for many patients, such as prison populations and intravenous drug

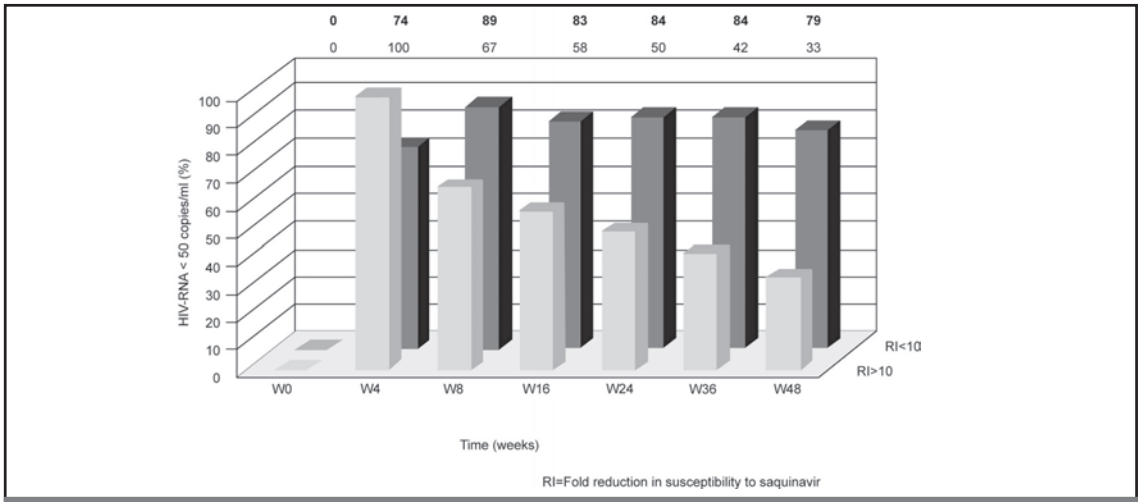

Figure 2. *Proportion of patients with viral load < 500 copies/ml according to phenotypic resistance at baseline[17].*

users, and may improve adherence by fitting in with their lifestyles. Once-daily antiretroviral therapy with the boosted PI saquinavir/ritonavir combination (1,600 mg/100 mg) would, therefore, be an important treatment option for these patients. Table 2 provides a summary of the clinical studies, which have evaluated a once-daily combination. These studies provide encouraging efficacy and safety results.

The largest of these studies (FOCUS) was undertaken to investigate the effects of saquinavir-SGC/ritonavir 1,600 mg/100 mg or efavirenz 600 mg once daily, in combination with two NRTIs, in 154 antiretroviral-*naïve* patients (Table 2)[19]. At 24 weeks, 60 and 78% of the ITT population in the saquinavir/ritonavir and efavirenz arms of the study, respectively, exhibited HIV-RNA values < 50 copies/ml[19]. When only the patients who were receiving treatment were evaluated (OT population), viral suppression between the treatment arms was similar –83 and 90%, respectively. For HIV-RNA values < 400 copies/ml, 97 and 94% of patients in the saquinavir/ritonavir and efavirenz arms, respectively, had effective viral suppression (OT population). Comparable increases in CD4+ cell count were also observed in both treatment groups. The difference in efficacy results in the ITT analysis is believed to be due to the higher than expected discontinuation rate in the saquinavir/ritonavir arm of the study. There were 21 patients in the saquinavir/ritonavir arm who withdrew compared with 12 patients in the efavirenz arm who withdrew from the ITT population in the first 24 weeks. Withdrawal was primarily due to adverse events in the saquinavir/ritonavir arm (15/21 patients), with the events most commonly being gastrointestinal in nature (nausea or vomiting). However, more grade 3/4 laboratory abnormalities in triglycerides (> 750 mg/dl or 8.4 mmol/l) were reported in the efavirenz group (4%) compared with the saquinavir/ritonavir group (1%)[19]. Extended data on the durability of the viral response and safety will be provided by the 48-week data. It is likely that use of the HGC formulation of saquinavir may lower the incidence of gastrointestinal adverse events observed in the saquinavir arm of this study[12].

There is evidence that saquinavir/ritonavir 1,600 mg/100 mg once daily is also of benefit in antiretroviral-experienced patients. An open-label study was conducted to evaluate the efficacy and safety of this regimen in 69 antiretroviral-experienced patients with a plasma viral load < 50 copies/ml after long-term treatment with saquinavir 1,400 mg BID plus two NRTIs (Table 2). These patients were switched to a saquinavir/ritonavir 1,600 mg/100 mg once-daily regimen while continuing their NRTIs. At 48 weeks, 63/69 patients (91%) still had a plasma viral load < 50 copies/ml. In five of the remaining six patients, plasma viral load was < 400 copies/ml at week 48, while one patient had an unexplained rise in viral load (to 39,500 copies/ml) that fell to < 50 copies/ml 12 weeks later[13]. An increase in CD4+ cell count was also seen, which was significantly greater than that seen during the previous year on saquinavir BID ($p < 0.001$)[20] (Fig. 3). Saquinavir/ritonavir was well tolerated and no patients changed treatment. No significant change in the median plasma triglyceride concentration was seen following the switch[20].

A once-daily boosted saquinavir/ritonavir treatment regimen that includes efavirenz has been evaluated in antiretroviral-experienced (two NRTIs plus PI or non-nucleoside reverse transcriptase inhibitors [NNRTI]) patients with extensive resistance to NRTIs. In this study, involving 42 patients, saquinavir/ritonavir 1,200 mg/100 mg plus efavirenz 600 mg were administered once daily (Table 2). After 1 year, 71.4% (30/42) of these patients had viral suppression (< 50 copies/ml)[21]. The authors concluded that this may be a valuable treatment option for patients unable to take NRTIs because of toxicity, as well as for those with extensive NRTI resistance.

Eighteen PI-*naïve* (treatment-*naïve*) and 17 PI-experienced subjects (NRTI pre-treated) were in-

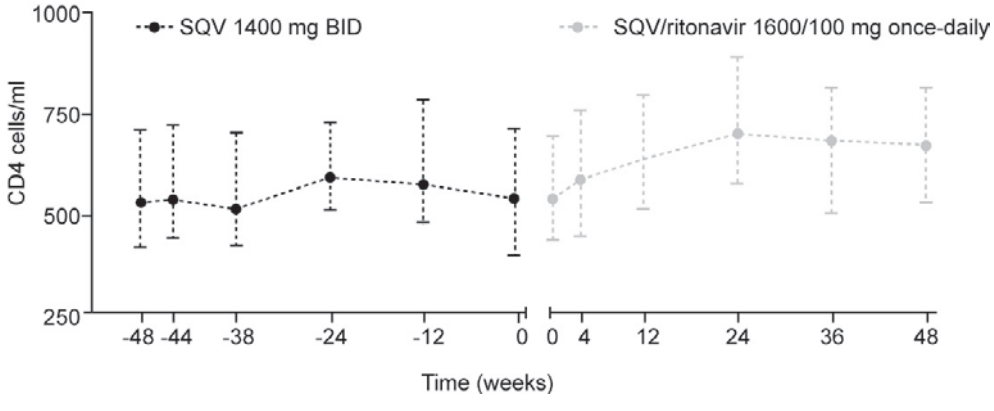

Figure 3. *CD4+ cell count for patients receiving saquinavir 1,400 mg BID and saquinavir/ritonavir 1,600 mg/100 mg once daily (median change from baseline)[13].*

volved in a prospective, open-label, non-comparative multicentre study evaluating the addition of once-daily saquinavir/ritonavir 1,600 mg/100 mg to dual NRTI therapy (Table 2)[22]. In the PI-*naïve* patients following 3 months of therapy, plasma HIV-RNA had fallen by 2.70 $\log_{10}$ copies/ml from 4.97 $\log_{10}$ copies/ml at baseline. In the PI-experienced patients, HIV–RNA levels following 3 months of therapy remained below the baseline level of 2.3 $\log_{10}$ copies/ml[22]. The regimen was well tolerated in all patients.

Encouraging results with once-daily saquinavir/ritonavir (1,600 mg/200 mg) were also seen in patients who previously failed a HAART regimen including saquinavir 600 mg TID (Table 2)[23]. Of a total of 18 patients, 12 were followed up for at least 12 weeks, and their viral load fell to < 200 copies/ml. More importantly, this drop in viral load was seen in 4/10 patients with the L90M mutation at baseline[23].

Overall, these studies show that the administration of saquinavir/ritonavir once daily as part of antiretroviral therapy provides potent and durable HIV RNA suppression.

'Double boosting' of saquinavir

The application of 'double boosting' is being investigated as a salvage treatment option for PI-experienced patients with multiclass drug resistance (Fig. 4). The results of studies of this therapy are shown in table 3.

The combination of lopinavir/ritonavir 400 mg/100 mg BID plus saquinavir 1,000 mg BID (plus 2 NRTIs) resulted in increased saquinavir exposures. This was found to have positive benefits at up to 24 weeks in the salvage setting[27]. More importantly, clinical data from the PIE (Protease Inhibitor Experienced) study has demonstrated effective viral load suppression with this combination in a population of HIV patients with limited remaining treatment options[28]. In 28 PI-experienced (with a mean of almost of 3 PIs), lopinavir-*naïve* patients, 24-week results showed that 88% (19/21) of patients had effective viral load suppression (< 400 copies/ml) compared with baseline median HIV-RNA values of 31,100 copies/ml. The regimen was well tolerated, with grade 3/4 increases in cholesterol and triglycerides occurring in only 3 patients. The authors concluded that the high levels of exposure achieved with the double boosted PIs may be beneficial for those patients with extensive drug resistance.

A further salvage study is currently being conducted administrating lopinavir/ritonavir 400 mg/100 mg BID plus saquinavir 1,000 mg BID with three NRTIs[29]. In an interim analysis of this combination in 24 HIV-infected patients, 36% of patients had a plasma viral load of < 80 copies/ml at 24 weeks[29]. In addition, the regimen was well tolerated.

Finally, a double-boosted PI regimen of lopinavir/ritonavir plus saquinavir that does not include NRTIs has also been recently reported[30].

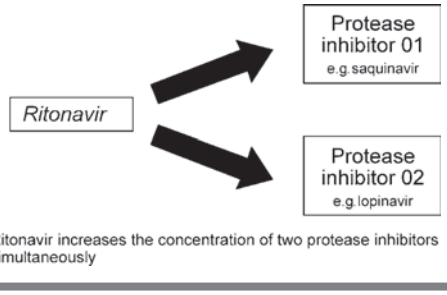

Figure 4. *Concept of double boosting*

This regimen may be appropriate for patients with nucleoside toxicity as well as for patients with NRTI resistance. In this study, involving 27 patients (14 with multiple NRTI resistance, 11 with nucleoside toxicity and two with both resistance and toxicity), BID doses of lopinavir/ritonavir 400 mg/100 mg plus saquinavir 1,000 mg were administered. After a median follow-up of 17 weeks (range 5-62 weeks), 24/27 patients were still on therapy. Median CD4+ cell count had increased by 73 cells/mm^3 from baseline and viral load decreased by a median 2.7 log. Pharmacokinetic profile monitoring of all patients after a minimum of 14 days on this regimen indicated that lopinavir/ritonavir coadministration effectively boosted saquinavir levels, with no adverse drug interactions between the two PIs. The authors concluded that a NRTI-sparing double-boosted PI regimen of saquinavir plus lopinavir/ritonavir may provide a valuable treatment option.

A number of factors make the combination of amprenavir/saquinavir/ritonavir a logical prospect for PI double boosting. Isolates with multiple protease inhibitor mutations often retain susceptibility to amprenavir and saquinavir, and different key resistance mutations have been identified for these two agents[31]. In addition, a potential for antiviral synergy has been demonstrated between these agents[32]. However, an evaluation of the combination lopinavir/amprenavir/ritonavir in salvage therapy revealed a reciprocal drug-drug interaction, resulting in a decrease in amprenavir and possibly lopinavir concentrations rather than the anticipated increase in amprenavir levels[22].

Future approaches with boosted saquinavir

There is new evidence to suggest that saquinavir boosting can be achieved with the investigational once-daily PI atazanavir. Importantly, this combination appears to have a favourable impact on lipid profiles[33]. In a recent study of 85 patients who failed prior PI antiretroviral therapy and were then randomized to a once-daily saquinavir/atazanavir (1,200 mg/400 mg or 1,200 mg/600 mg) or BID saquinavir/ritonavir (400 mg/400 mg) regimen, durable suppression of HIV-

Table 3. *Clinical efficacy data available on 'double-boosted' saquinavir plus lopinavir/ritonavir regimens (includes all available data at time of publication)*[27-30]

Reference	Study design	Treatment regimen	Patient numbers and characteristics	Median baseline HIV RNA level (log_{10} copies/ml) and CD4+ cell count (cells/μl)	Main efficacy results
Smith, et al., 2001	Prospective, open-label, single-arm	SQV 1,000 mg BID plus LPV/RTV 400 mg/100 mg BID plus NRTIs (EFV 600 mg once daily added at week 4 in unresponsive patients)	ARV experienced (n = 36)	RNA = 5.1 CD4+ = 91	**4 weeks** HIV-RNA drop of ≥ 0.8 log_{10} = 61% CD4+ increase of 16 cells/mm^3
Hellinger, et al., 2002	Prospective, open-label, single arm, dose escalation	Initiated SQV 1,000 mg BID plus LPV/RTV 400 mg/100 mg BID plus two or more NRTIs (doses individualised guided by virtual phenotype results)	LPV-*naïve*, PI-experienced (n = 28)	RNA >1000 copies/ml	**24 weeks** HIV-RNA < 400 copies/ml: 68% (ITT), 87% (OT) HIV-RNA < 50 copies/ml: 42% (ITT), 53% (OT)
Ruiz, et al., 2002	Prospective, open-label	SQV 1,000 mg BID plus LPV/RTV 400 mg/100 mg BID plus three NRTIs	ARV-experienced (n = 24)*	RNA = 4.3* CD4+ = 322*	**24 weeks** HIV-RNA < 80 copies/ml: 36%
Staszewski, et al., 2002	Prospective, open-label	SQV 1,000 mg BID LPV/RTV 400 mg/100 mg BID	All ARV-experienced: NRTI resistant, (n = 14); NRTI toxicity (n = 11); NRTI resistance and toxicity (n = 2)	RNA 113,000 copies/ml CD4+ = 192	**Median 17 weeks (range 5-62)** Median CD4+ increase of 73 cells/mm^3 Median HIV-RNA decrease of 2.7 log

SQV = saquinavir
RTV = ritonavir
LPV = lopinavir
EFV = efavirenz
NRTI = nucleoside reverse transcriptase inhibitor
ITT = intention to treat analysis
OT = on treatment analysis
ARV = antiretroviral

**Patients without a treatment interruption prior to therapy*

RNA and increases in CD4+ cell counts were observed with all three treatment regimens after 48 weeks. More importantly, total cholesterol, fasting triglycerides and fasting low density lipoprotein cholesterol levels all fell in both saquinavir/atazanavir arms, a decrease that was not seen in the saquinavir/ritonavir arm. This favourable lipid profile suggests that a saquinavir/atazanavir PI combination may be an ideal boosted PI regimen, which can be taken once daily.

Summary

The clinical data presented in this review confirm that boosted saquinavir regimens provide potent and sustained viral suppression. In addition, double boosting (currently using saquinavir 1,000 mg plus lopinavir/ritonavir 400 mg/100 mg BID) may become increasingly important, particularly in the salvage setting. Importantly, no upper limit to the therapeutic window of saquinavir has been identified to date, and consequently this increased efficacy is not to the detriment of patient tolerability.

The HGC formulation of saquinavir appears to be better tolerated than the SGC formulation, with less gastrointestinal disturbance[11,12,34]. Now the introduction of boosting with ritonavir has overcome the issues of poor bioavailability with the HGC formulation[11,12], this may now be the preferred formulation.

In conclusion, boosted saquinavir/ritonavir provides potent and sustained viral suppression. Furthermore, it is likely to be one of the better tolerated boosted PIs, as the increased benefits do not compromise patient tolerability. In particular, only minimal effects on serum lipids are seen with boosted saquinavir regimens[18,19]. Since lack of tolerability inhibits long-term treatment success by limiting adherence with therapy[35,36], regimens with improved tolerability are likely to be of particular value.

Saquinavir/ritonavir, either as a BID (1,000 mg/100 mg), once daily (1,600 mg/100 mg) or double-boosted (1,000 mg plus lopinavir/ritonavir 400 mg/100 mg) regimen, therefore, has an important role to play in achieving effective viral suppression in the long-term, meeting vital patient needs.

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