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Saquinavir Soft Gelatin Capsule

A Comparative Safety Review

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Contents

Abstract

The HIV-1 protease inhibitor (PI) saquinavir is available as a soft gelatin capsule (SGC) formulation. At the recommended dosage of saquinavir SGC (1200mg 3 times daily), this formulation provides around 8-fold greater exposure than the established hard gelatin capsule (HGC) formulation at the recommended dosage of 600mg 3 times daily.

As with the HGC formulation, the most common adverse events seen with saquinavir SGC are gastrointestinal symptoms (e.g. diarrhoea, abdominal discomfort and nausea). Some of these may occur with a slightly higher frequency with the SGC than with the HGC formulation. Saquinavir SGC has only a minimal effect on nonfasting serum lipid and cholesterol levels.

Like other PIs, saquinavir is metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme and is susceptible to interactions with inducers (e.g. rifabutin and rifampicin) and inhibitors (e.g. clarithromycin and ketoconazole) of this enzyme. Ritonavir, nelfinavir, indinavir and delavirdine, all CYP3A4 inhibitors, greatly increase saquinavir plasma concentrations and the therapeutic implications of these interactions continue to be evaluated. While saquinavir is the least potent CYP 3A inhibitor among the PIs, several drugs (notably terfenadine, astemizole and cisapride) should not be given in combination with saquinavir.

Therefore, although the SGC formulation enhances saquinavir exposure, it has a similar safety profile to the HGC formulation.

Saquinavir, formulated as the hard gelatin capsule (HGC) formulation, was the first HIV protease inhibitor (PI) to be approved for the treatment of HIV infection. When used in combination with other antiretrovirals, saquinavir HGC has been demonstrated to provide a survival advantage,[1-4] although the poor bioavailability of this formulation means that it is less effective than the other currently licensed PIs. Subsequently, saquinavir has been reformulated as an enhanced soft gelatin capsule (SGC), resulting in increased drug exposure and enhanced antiretroviral activity compared with the HGC formulation.[5,6] The currently recommended dosage of saquinavir SGC, 1200mg 3 times daily, provides around 8-fold greater exposure than the recommended dosage of the HGC formulation (600mg 3 times daily), as quantified by the area under the curve to 24 hours(AUC_{0-24h}).[6]

This review focuses on the safety profile of saquinavir SGC and compares it with the safety profiles of other PIs. Pertinent data concerning the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine, nevirapine and efavirenz, and the reverse transcriptase inhibitors (NRTIs), including abacavir, are also considered. The review incorporates data from published literature sources (e.g. MEDLINE), case reports, conference abstracts and prescribing information. Information was selected on the basis of relevancy to the subject and the most pertinent and recent data was cited as far as practicable.

1. Adverse Events

Although the SGC formulation provides significantly greater systemic saquinavir exposure than the HGC formulation, the nature of adverse events with the 2 formulations is similar (table I).[3,5,7-10] The adverse events associated with both saquinavir formulations are well characterised and mainly involve gastrointestinal symptoms. Laboratory abnormalities include decrease in blood glucose level (6%) and increases in creatine phosphokinase (4%), alanine amino transferase (3%) and aspartate aminotransferase (4%) activities.[8]

Comparative studies using currently recommended dosages have shown that certain gastrointestinal events (e.g. dyspepsia, and abdominal pain or discomfort) occur with a slightly higher frequency with saquinavir SGC than with the HGC formulation (table I).[6,8,10] However, most adverse events were mild and few required discontinuation of treatment. Data from a long term, comparative study of the 2 formulations indicates that the range and frequency of common adverse events in saquinavir SGC recipients does not increase over time.[10] The incidence of the most common adverse events (nausea, diarrhoea, flatulence and abdominal discomfort) ranged from 12 to 18% after 16 weeks of treatment to 7 to 12% at 72 weeks in an as-treated analysis.[11]

The tolerability and safety of saquinavir SGC 1200mg 3 times daily was assessed in a large, open-label, noncomparative, 48-week safety study involving 442 patients.[7] Most patients were also taking 2 NRTIs, mainly lamivudine (73%) or zidovudine (65%); fewer patients used stavudine (32%), zalcitabine (12%) or didanosine (12%). The most common adverse events of at least moderate intensity considered possibly related to saquinavir, were diarrhoea (20%), nausea (11%), abdominal discomfort (9%), dyspepsia (8%) and flatulence (6%). Severe adverse events were infrequent and included vomiting (3%) and abdominal pain (2%). Other com-

Table I. Number (percentage) of patients experiencing clinical adverse events[a] possibly related to saquinavir hard gel capsule (HGC) 600mg 3 times daily or soft gel capsule (SGC) 1200mg 3 times daily during a comparative study of 16 weeks' duration (reproduced from Mitsuyasu et al.[6] with permission)

Adverse event	Saquinavir HGC (n = 81)	Saquinavir SGC (n = 90)
Digestive system complaint	25 (30.9)	40 (44.4)
nausea	11 (13.6)	16 (17.8)
diarrhoea	10 (12.3)	14 (15.6)
flatulence	6 (7.4)	11 (12.2)
abdominal discomfort	4 (4.9)	12 (13.3)
abdominal pain	1 (1.2)	7 (7.8)
dyspepsia	0	8 (8.9)
Fatigue	5 (6.2)	6 (6.7)
Headache	4 (4.9)	8 (8.9)

a Occurring in ≥5% of patients.

mon adverse events, occurring in ≥5% of patients, were headache and fatigue.

Gastrointestinal disturbances are among the most common adverse events associated with all available PIs, including ritonavir,[12,13] nelfinavir[14-16] and amprenavir.[17] In randomised, long term, comparative studies of PIs administered in combination with 2 NRTIs, the incidence of gastrointestinal adverse events with saquinavir SGC 1200mg 3 times daily was similar to that observed with indinavir 800mg 3 times daily[18] or nelfinavir 750mg 3 times daily, although diarrhoea was more common with nelfinavir.[19] Interestingly, addition of saquinavir SGC to nelfinavir monotherapy did not increase the incidence of diarrhoea.[19]

In clinical trials to date, 8 to 15% of patients receiving saquinavir SGC for up to 72 weeks have discontinued treatment because of adverse events.[7,8,10,19] These rates are lower than those reported from studies of ritonavir over 52 weeks (21%),[13] similar to those reported with indinavir up to 100 weeks (3 to 11%),[18,20,21] and slightly higher than those reported with nelfinavir up to 72 weeks (1 to 5%).[9,14,15]

2. Lipodystrophy Syndrome

Reports of a lipodystrophy syndrome occurring during antiretroviral therapy including a PI have raised concerns over the long term tolerability of these agents.[22–28] The syndrome is characterised by abnormal fat distribution, and may include signs such as peripheral fat wasting (e.g. in the extremities, buttocks and face), central adiposity (with breast enlargement in women) only, or cervical fat pad enlargement ('buffalo hump'). These changes may be accompanied by hyperlipidaemia (increased serum levels of cholesterol and triglycerides) and insulin resistance, although diabetes mellitus is uncommon. While no causal role of PIs has been firmly established, these agents have been implicated in several aspects of fat handling, including inhibition of cytoplasmic retinoic acid binding protein type-1 (CRAP-1)[29] and inhibition of the muscle glucose transporter Glut-4.[30] One study showed that physical signs of lipodystrophy were significantly more common in patients infected with HIV (98% men) treated with PIs (indinavir or saquinavir plus ritonavir) than in PI-naïve patients (64 *vs* 3%, respectively; p = 0.0001), as were the associated metabolic abnormalities.[22] In addition, the incidence of lipodystrophy has been correlated with the duration of PI therapy.[22,23,25]

Individual PIs differ in their effects on serum lipid profiles and the limited evidence available suggests that they may also have different propensities to cause lipodystrophy. Ritonavir causes hyperlipidaemia (particularly increased triglyceride levels) more commonly than indinavir, nelfinavir and saquinavir.[13,31-36] Cameron et al.[13] reported that 12.9% of patients (n = 541) treated with ritonavir 600mg twice daily developed grade IV elevated fasting serum triglyceride levels of above 16.9 mmol/L (1496 mg/dl), compared with 0.4% of placebo recipients (n = 545). By comparison, saquinavir has a limited effect on serum glucose, lipid and cholesterol profiles (figs 1a, 1b & 1c),[3,5-8,34-38] and appears to be associated with a lower frequency of lipodystrophy than the other PIs.[39]

Perhaps not surprisingly, lipodystrophy was shown to be more common (relative risk 1.70) and pronounced in patients receiving dual PI therapy with saquinavir plus ritonavir compared with indinavir alone.[22] Ritonavir would appear to make the greater contribution to this effect: results from a recent cross-sectional survey of patients receiving different PIs suggest that the incidence of lipid disturbance with saquinavir SGC is no greater than that in PI-naïve patients, and lower than that with ritonavir.[40] However, such tolerability advantages may well be negated in clinical practice, given that ritonavir is now routinely added to most PI-based regimens to enhance the drug's systemic bioavailability. Another study showed abnormal fat accumulation to be significantly more common in indinavir recipients (24 out of 77 patients; 31%) compared with patients receiving other PIs, mainly saquinavir HGC and/or ritonavir (5 out of 38 patients; 13%; p = 0.03).[23] Indeed, in this study the relative risk of lipodystrophy with indinavir was almost 4-fold higher than that with other PIs.

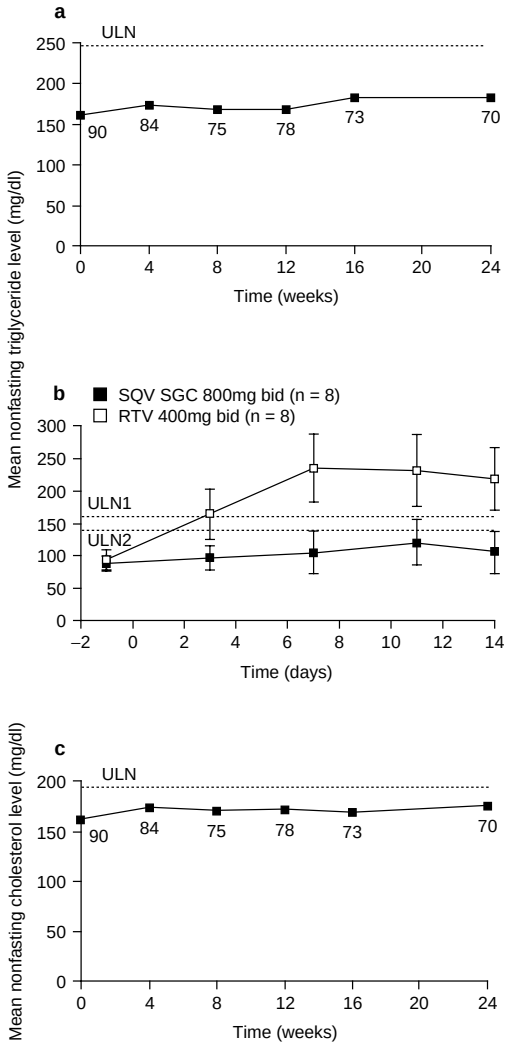

Fig. 1. (**a**) Effect of saquinavir soft gelatine capsule (SQV SGC) on mean, nonfasting serum triglyceride levels in patients infected with HIV (reproduced from Skolnik et al., [37] with permission). The dashed line on the figure denotes the upper limit of normal (ULN). The total number of patients at each data point is indicated on the graph. (**b**) Effects of SQV SGC and ritonavir on mean fasting serum triglyceride levels (± standard error of the mean) in healthy volunteers (reproduced from Nauss-Karol et al.,[38] with permission). The ULN range used was 140 to 160 mg/dl for triglycerides. (**c**) Effect of SQV SGC on mean, nonfasting serum total cholesterol levels (reproduced from Skolnik et al.,[37] with permission). **bid** = twice daily; **RTV** = ritonavir.

Although the occurrence of lipodystrophy-type syndromes in patients infected with HIV has received much attention recently, cases have also been reported in PI-naïve patients[41-45] and in patients receiving only NRTIs,[42,46-51] indicating that a single causative factor is unlikely to be identified.[52] Preliminary results from the Lipodystrophie Cohorte (LIPOCO) study, evaluating fat distribution and metabolic abnormalities in patients infected with HIV undergoing antiretroviral therapy suggest that there may be 3 major types of fat distribution abnormalities.[47] These include fat depletion which may be related to the use of stavudine, fat redistribution related to a side-product of effective virus control (although this idea is refuted by others[53,54]) and a subcutaneous adiposity syndrome resulting from an increased caloric intake.[52] This study also indicated that the use of the PIs was not significantly associated with fat wasting or fat distribution abnormalities. Therefore some workers have suggested that combined endocrine and metabolic abnormalities (e.g. hyperlipidaemia, increased free fatty acid levels, glucose intolerance and testosterone abnormalities) may affect regional lipid metabolism and body-fat distribution in patients infected with HIV.[48] Some researchers have attributed the bodyweight gain typically associated with a therapeutic response to HIV therapy to this phenomenon.[55]

3. Drug Interactions

Patients infected with HIV are routinely treated with combinations of antiretroviral agents. They also receive a variety of additional adjunctive therapies, such as those used to prevent or treat opportunistic infections. Interactions between antiretroviral agents or between antiretrovirals and concomitant medications are of significant clinical concern because they may increase the incidence, severity and range of adverse events.

In common with other PIs,[56-60] saquinavir is metabolised by the cytochrome P450 (CYP) system (primarily the CYP3A4 isoform) in the intestine and liver.[5,61] Drugs that induce CYP3A isoforms, such as rifabutin and rifampicin, may reduce saquin-

Table II. Drugs that affect saquinavir soft gel capsule plasma concentrations.[61,62,63]

Effect	Drug (% change in AUC)	Necessary action
Decrease saquinavir plasma concentrations	Antimycobacterials: rifampicin (84%), rifabutin (43%)	Avoid/use alternative agents where possible
	NNRTIs: efavirenz (62%), nevirapine (24%)	Not recommended with saquinavir as sole PI
Increase saquinavir plasma concentrations	Antibacterials: clarithromycin (177%)	None
	Antifungals: ketoconazole (130%)	None
	Histamine H_2 antagonists: ranitidine (67%)	None
	PIs: indinavir (364%; 1200mg dose of indinavir), nelfinavir (392%), ritonavir (1589-2158%)	Interactions used therapeutically (may need to modify saquinavir dose)
	NNRTIs: delavirdine (5-fold)	May need to modify saquinavir dosage

AUC = area under the plasma concentration-time curve; **NNRTIs** = non-nucleoside reverse transcriptase inhibitors; **PI** = protease inhibitor.

avir plasma concentrations (table II), leading to decreased antiviral activity.[64] The effects of rifabutin and rifampicin are especially relevant, as these drugs are often used to treat mycobacterial opportunistic infections in patients infected with HIV. Concurrent use of these agents with PIs, including saquinavir, is not recommended.

Conversely, the metabolism of saquinavir may be reduced by concurrent administration of non-antiretroviral drugs that inhibit CYP3A enzymes (table II). Interactions of particular relevance in patients infected with HIV are those with the macrolide antibacterial clarithromycin, used to treat *Mycobacterium avium* complex and routine bacterial infections, and antifungals such as ketoconazole.[3,5,64] However, the resulting increases in saquinavir plasma concentrations are generally not expected to lead to clinically significant changes in tolerability and do not necessitate avoidance of these agents or saquinavir dosage reduction.

All available PIs inhibit the CYP3A system to some extent. Ritonavir potently inhibits CYP3A-mediated metabolism of saquinavir *in vitro*.[65] In humans, coadministration of ritonavir produces marked and sustained increases in plasma concentrations of saquinavir[62,64-69] and other PIs.[65,70,71] This interaction forms the basis for the clinical use of saquinavir plus ritonavir as a dual PI-component of antiretroviral therapy. Typical dosages are saquinavir 400mg twice daily plus ritonavir 400mg twice daily. For the HGC formulation, these dosages give maximum plasma drug concentration (C_{max}) and AUC values for saquinavir that are 13- and 16-fold higher than for saquinavir HGC given at 600mg 3 times daily.[5] Administration of saquinavir SGC plus ritonavir each at 400mg twice daily results in a 2.2-fold increase relative to saquinavir SGC given at 1200mg 3 times daily. These increases in saquinavir exposure have benefit in terms of reduced interpatient variation and increased clinical efficacy. In terms of tolerability, the combination of saquinavir plus ritonavir at 400mg twice daily is not necessarily optimal. Ritonavir is commonly associated with gastrointestinal disturbances, asthenia, circumoral paraesthesia and headache, events that are more problematic than those commonly experienced with saquinavir.[12] However, it is particularly striking that a reduction in the dosage of ritonavir can maintain a significant increase in saquinavir exposure whilst improving the tolerability profile of the combination. For example, ritonavir 200mg, when administered in combination with saquinavir 800mg, is associated with a 10-fold increase in saquinavir exposure, yet has no apparent effect on tolerability.[64] Higher doses of ritonavir (300mg and 400mg) in combination with saquinavir 800mg also substantially increase saquinavir exposure, but there is a concurrent increase in adverse events (table III). Studies using saquinavir HGC (600mg single dose or 3 times daily) have shown that ritonavir (200mg single dose or 300mg twice daily) increases the AUC of saquinavir by at

Table III. Pharmacokinetics and tolerability of saquinavir (SQV) soft gelatin capsule (SGC) and ritonavir (RTV) alone or in combination (reproduced from Buss[64], with permission)

No. of patients evaluable for safety assessment[a]	Dosage (twice daily)		Day 14 AUC_{24} (μg • h/L)		No. of patients experiencing at least 1 AE	Adverse events	
	SQV SGC	RTV	SQV SGC	RTV		Total no. of events	Most common events[b] (no. patients reporting event)
8	800		4.6		5	19	Headache (2), sore throat (2), increased sweating (2)
8	800	200	56.8	36.4	5	17	Headache (2), constipation (2)
8	800	300	67.9	58.6	7	37	Oral hypoaesthesia (5), hypoaesthesia of the tongue (2), headache (2), weakness (2), circumoral paraesthesia (2), sore throat (2)
9	800	400	71.0	76.6	7	57	Oral hypoaesthesia (5), taste disturbance (4), headache (4), weakness (2), nausea (6), vomiting (2), dizziness (2), feeling hot (2), pyrexia (2), sore throat (2), cough (2)
8		400		87.1	7	35	Oral hypoaesthesia (5), headache (5), hypoaesthesia of the tongue (3), taste disturbance (2), nausea (3), rhinitis (2)

a 8 patients were evaluable for pharmacokinetics in all groups.

b Adverse events reported by more than 1 patient (of any severity and any relationship to treatment).

AE = adverse event; **AUC** = area under the plasma concentration-time curve.

least 50-fold.[65,67,68] Research is currently ongoing to determine the optimal combination of saquinavir SGC plus ritonavir.

After ritonavir, indinavir is the second most potent CYP3A inhibitor, followed by nelfinavir and amprenavir.[59,72-76] Indinavir and nelfinavir also greatly increase plasma concentrations of saquinavir,[5,70,77] while preliminary data suggest amprenavir has no clinically significant effect on saquinavir pharmacokinetics.[78]

Saquinavir is the least potent CYP3A inhibitor and would not be expected to have a clinically relevant effect on other isozymes of the CYP enzyme system.[59,72,73,75,76,79] Nevertheless, saquinavir may increase concentrations of certain drugs such as terfenadine, astemizole and cisapride, which are metabolised by CYP3A. In 1 study, saquinavir SGC 1200mg 3 times daily increased the AUC of terfenadine 60mg twice daily almost 4-fold.[5] Therefore, in view of the risk of cardiac arrhythmias associated with detectable plasma concentrations of these agents, they should not be coadministered with saquinavir SGC[3,5] or any other PI. Coadministration of certain other CYP3A-metabolised drugs (summarised in figure 2) should also be avoided.

Saquinavir has no clinically significant effects on plasma concentrations of ritonavir[63,71] or nelfinavir.[5,16] Saquinavir does not significantly affect the pharmacokinetics of the NRTIs zidovudine and zalcitabine or the NNRTIs delavirdine and nevirapine.[5] Like most other PIs, saquinavir is highly bound to circulating plasma proteins (approximately 97%). However, in view of its high therapeutic index and large volume of distribution, interactions involving its displacement from plasma proteins are unlikely to be of clinical relevance.[5]

Qualitatively, indinavir[81] and nelfinavir[16] have drug interaction profiles broadly similar to that of

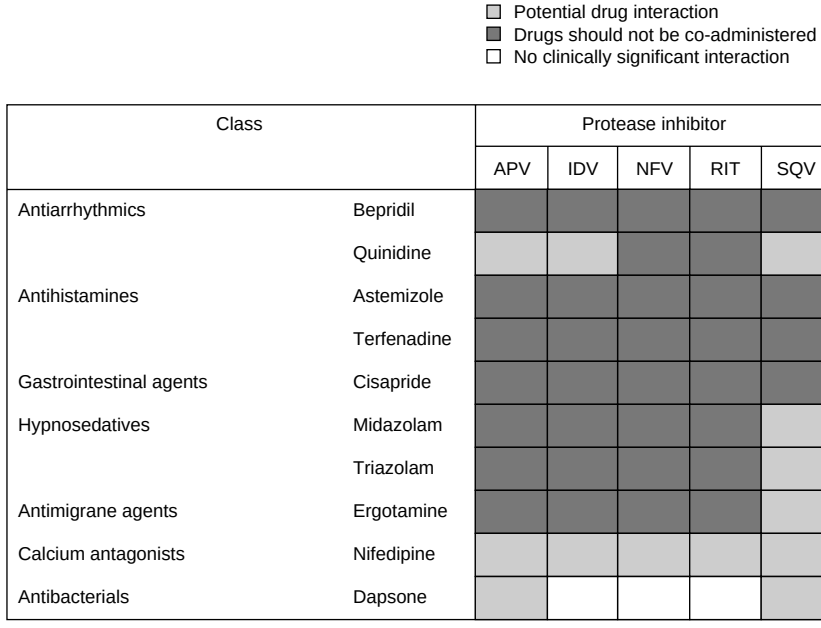

Fig. 2. Drugs whose plasma concentrations may be increased by saquinavir in comparison with other protease inhibitors, and which should be avoided or monitored in patients treated with saquinavir.[80] **APV** = amprenavir; **IDV** = indinavir; **NFV** = nelfinavir; **RIT** = ritonavir; **SQV** = saquinavir.

saquinavir, although quantitatively indinavir, in particular, has a potentially greater effect on the pharmacokinetics of CYP3A-metabolised drugs. Only limited drug interaction data are available for amprenavir, but these also suggest a profile similar to that of saquinavir.[78,82]

The NNRTIs have varying potentials for drug interaction with saquinavir. Delavirdine is metabolised by CYP3A and is also a potent inhibitor of this isoform.[83] When given in combination, it increases the exposure of saquinavir 5-fold.[84] Nevirapine, however, induces CYP3A and reduces plasma concentrations of saquinavir.[85] The NNRTI efavirenz is primarily metabolised by CYP3A.[86] Efavirenz induces CYP3A *in vivo* and considerably decreases the C_{max} and AUC of saquinavir coadministered as SGC.[87] Consequently, combination therapy with efavirenz and saquinavir as the sole PI is not recommended. Of the newly introduced antiretrovirals, abacavir is not CYP-metabolised and, as it does not inhibit the major CYP isoforms *in vitro*, appears unlikely to interact with drugs that do.[88]

4. Implications for Patient Management

Saquinavir SGC is generally well tolerated when combined with other antiretrovirals, and its adverse event profile permits long term treatment of patients infected with HIV. Despite increasing the total daily exposure to saquinavir, reformulation of saquinavir as SGC has not greatly affected the adverse event profile of the drug, with gastrointestinal symptoms remaining the most common complaints. An important aspect of this profile is its predictability. This enables physicians to counsel patients about potential adverse events before treatment is initiated; such patients may be more likely to remain adherent if adverse events occur. In contrast, certain adverse effects of other anti-

retrovirals (e.g. abacavir-induced hypersensitivity) cannot be predicted in individual patients.

Concerns over lipodystrophy have recently dominated the issue of PI tolerability. Further research to characterise this syndrome is required, but evidence that is beginning to emerge suggests that the incidence of lipodystrophy is lower in patients taking saquinavir than some other PIs. Rather better documented is that saquinavir has a relatively low propensity for adverse drug interactions, making it straightforward for physicians to prescribe and patients to take.

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