



Ritonavir - An effective drug against HIV

JK Grover*
Vikrant Vats

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SS Rathi*

ABSTRACT

The new HIV protease inhibitors are likely to represent a major advance in the treatment of HIV infection, particularly when used in combination with other anti-retroviral agents. The addition of ritonavir to the standard drug regimen of patients with HIV infection has resulted in decreased mortality and has been shown to slow down the clinical progression of disease as compared to placebo recipients. Although the drug was well tolerated and was not associated with any serious adverse reaction, data from long-term trials is eagerly awaited to corroborate the safety of ritonavir. The problem with other anti-retroviral agents is the emergence of resistance, which is responsible for their waning efficacy. Although resistance has been seen with ritonavir, it arises as a result of multiple mutations, which produces a stepwise increment in resistance. This very complex pattern of resistance explains the absence of rapid appearance of resistant mutants with ritonavir. Moreover, the resistance between ritonavir and saquinavir is not over-lapping, and therefore the combination of these drugs is an attractive proposition especially as ritonavir improves the bioavailability of saquinavir. As such, ritonavir may become an important component of the combination regimen to treat advanced as well as less advanced HIV infection.

Keywords: Ritonavir; anti-retroviral agents; HIV infection.

INTRODUCTION

Ritonavir is a protease inhibitor (approved for the treatment of HIV infection) which has HIV-1 resistance profile similar to that of indinavir but different from saquinavir. In clinical trials in patients with HIV-1 infection, ritonavir caused an increase in CD4+ cell

counts with a marked reduction in viral load within 2 weeks of treatment. Results of 2 small clinical trials have been encouraging. Triple therapy of ritonavir plus zidovudine along with lamivudine or zalcitabine has been shown to reduce HIV viremia to below detectable levels in most patients with acute HIV

* All India Institute of Medical Sciences, New Delhi, India.

Address for Correspondence: Dr. JK Grover, Room No. 4017, Department of Pharmacology, AIIMS, Ansari-Nagar, New Delhi - 110029, India.

infections and in some patients with advanced HIV infection.

Aspartic protease is a critical enzyme that is involved in processing the products of the gag and gagpol genes into the functional core proteins and viral enzymes of HIV. Inhibition of HIV protease results in the release of noninfectious immature viral particles.^{1,2}

PHARMACODYNAMICS

In vitro anti-HIV activity

- In a human T cell line (MT-4), ritonavir and zidovudine inhibited 4 laboratory strains of HIV-1 at similar concentrations. However, ritonavir was 8 times less potent than zidovudine against HIV-2 strain.²
- The selectivity of ritonavir against HIV aspartic protease as compared to human aspartic protease was more (≥ 500 folds). The selectivity index (TC₅₀/IC₅₀) of ritonavir was approximately 1000.²

Clinical studies of anti-HIV activity

- In a study involving 20 patients, ritonavir caused a significant decrease in plasma HIV RNA levels. A two-week therapy with ritonavir 600 and 200 mg/day reduced the plasma HIV RNA levels by 11 and 275 folds respectively.³
- In another study, 17 out of 21 patients exhibited a drop in HIV RNA load from 2,64,600 copies/ml to below the limits of detection (10000 copies/ml). Moreover, ritonavir elevated the median CD 4+ count from 153 to 404 cells/ μ l after 2 to 14 (mean 6) weeks of

therapy. Simultaneous increase in CD8 + lymphocyte count also occurred as evident by elevation from 813 cells/ μ l at baseline to a peak of 1781 cells/ μ l. These changes in CD4+ and CD8+ lymphocyte suggested a decrease in viral load and antigenic stimulation.⁴

PHARMACOKINETIC PROFILE

The extent of oral absorption is high and is not affected by food. The clinically relevant $t_{1/2}$ β is about 3 to 5 hours. Because of autoinduction, plasma concentrations generally reach the steady state 2 weeks after the start of administration. The pharmacokinetics of ritonavir are relatively linear after multiple doses, with apparent oral clearance averaging 7 to 9 L/h.⁵ Ritonavir probably has a saturable metabolism as evident by the results of a fasting single dose study in 16 patients with HIV infection in which ritonavir 100 to 1000 mg showed a non-linear pharmacokinetic profile. Within the clinical concentration range, ritonavir is approximately 98 to 99% bound to plasma proteins, including albumin and alpha 1-acid glycoprotein. Cerebrospinal fluid (CSF) drug concentrations are low in relation to total plasma concentrations. Ritonavir is primarily metabolized by cytochrome P450 (CYP) 3A isoenzymes and, to a lesser extent, by CYP2D6. Four major oxidative metabolites have been identified in humans, but are unlikely to contribute to the antiviral effect.

About 34% and 3.5% of a 600 mg dose is excreted as unchanged drug in the faeces and urine, respectively. Ritonavir

is eliminated primarily by hepato-biliary process.⁶ For details see table I.

Table I

Pharmacokinetics Parameters ^{7,8}	Values
Maximum Plasma concentration after 600 mg twice daily for 3 weeks	11.2 mg/L
Time to maximum concentration	4 hr
Elimination half life	3-5 hr
Dosage & administration	Oral 600 mg twice daily

THERAPEUTIC TRIALS

Monotherapy

Two multi-centric, randomized, double-blind trials evaluated monotherapy with oral zidovudine (600-1200 mg/day) in patients with a CD4+count of ≤ 50 cells/ μ l. After 4 weeks of therapy, plasma HIV RNA load was considerably reduced in zidovudine recipients.^{7,9} In those who completed 12 weeks of therapy with this drug (i.e. 38%), the levels of plasma HIV RNA were reduced to below the limit of detection (10000 copies/ml).⁹ There was a significant increase in CD4 + cell count after four weeks of therapy including increase of > 200 cells/ μ l in some patients.^{7,9} However, after 4-12 weeks of treatment, HIV RNA levels returned towards baseline but this was less pronounced in patients receiving higher doses of zidovudine (1200 mg/day). These results can be interpreted in the light of emerging resistance to zidovudine monotherapy at suboptimal dosage.^{7,10}

Combination therapy^{8,11-14}

- In the phase III double blind trial, 1090 subjects received either zidovudine 600 mg (n=543) twice daily or placebo (n=547). Both the groups also received the current reverse transcriptase inhibitor treatment. Primary end points of the study were death, occurrence of AIDS defining illness, esophageal candidiasis, chronic hepatic ulcer and reoccurrence of *Pneumocystis carinii* pneumonia. The subjects were followed up for a mean of 6.1 (0.2-7.7) months. Twenty-six subjects (4.8%) receiving zidovudine and 46 (8.4%) receiving placebo died. The overall risk reduction was by 43%. The reduction in the incidence of AIDS defining illness or death was 56% (15.7 Vs 33.1%, $P<0.001$) in the zidovudine group.^{11,12} Health related quality of life (EuroQuol. Score) declined during the first week of zidovudine therapy but then gradually increased significantly after 20 weeks to 3.6 points, better than placebo group ($P<0.05$).¹⁴

Other clinical trials

- In another clinical trial, 356 untreated HIV patients received zidovudine 600 mg twice daily or zalcitabine 200 mg 3 times daily, either as monotherapy or in combination. As compared to zalcitabine monotherapy or zalcitabine zidovudine combination, the decrease in HIV RNA level was more in patients treated with zidovudine alone. In comparison with zalcitabine monotherapy, the elevation in the CD4+cell count was more in zidovudine

monotherapy and combination groups.¹⁵⁻¹⁷

- HIV was undetectable in 11 out of 12 men newly infected with HIV-1 who received 120 days of therapy with ritonavir (1200 mg/day), zidovudine (600 mg/day) and lamivudine (300 mg/day).¹⁸
- Patients with previously untreated advanced HIV infection (CD4 + count < 250 cells/ μ l) received triple therapy with ritonavir 1200 mg/day, zidovudine 600 mg/day and zalcitabine 2.25 mg/day. Mean CD4+counts rose from 170 cells/ μ l (baseline, n=32) to 327 cells/ μ l (after one year of treatment, n=17).¹⁹
- In a study, lymphocyte reconstitution was evaluated in 44 children (mean age 6.8 years) with HIV after ritonavir monotherapy followed by the addition of zidovudine and didanosine. After 4 weeks of therapy, there was a significant increase in CD4+ and CD8+ cells. CD4+ cells continued to increase, whereas CD8+ cells returned to baseline by 24 weeks. Unexpectedly, there was a significant increase in B cells. Early increase in lymphocytes after ritonavir therapy occurred due to recirculation, as shown by increases in B cells and CD4+, CD45RO and CD8+ cells.²⁰
- In another study, ritonavir was found to be useful in a significant proportion of HIV-infected children by improving the CD4 cell count and viral load.²¹
- In a monocentric retrospective study, 22 children with a minimum follow-up of 6 months under triple therapy including

ritonavir were analyzed for treatment efficacy. At entry, all the patients were protease inhibitor naive and all but two had received previous anti-retroviral therapy during a median period of 5 years. Their initial median CD4+ lymphocyte count and viral load were $121 \times 10(6)/l$ and 5.08 log₁₀ copies/ml, respectively. Median CD4 count increases were of $210 \times 10(6)/l$, $415 \times 10(6)/l$, and $472 \times 10(6)/l$ cells at 6, 12, and 18 months, respectively. There were median decreases of 1.14, 0.95, and 1.5 log₁₀ per ml of plasma in the concentration of viral RNA at 6, 12, and 18 months respectively. Seven patients maintained an undetectable viral load when under treatment. The introduction of at least one new reverse transcriptase inhibitor at the initiation of triple therapy correlated significantly with a greater viral suppression.²²

- Results of another multi-centric, randomized and open-label clinical trial conducted to evaluate the safety and anti-retroviral activity of ritonavir and saquinavir combination therapy in patients with HIV infection show that ritonavir (400 mg) combined with saquinavir (400 mg) twice daily with the selective addition of reverse transcriptase inhibitors is the best-tolerated regimen of four dose-ranging regimens and is equally as active as the higher dose combinations in HIV-positive patients without previous protease inhibitor treatment.²³

- Results of a study advocate the use of four-drug combination including 2 protease inhibitors (ritonavir and saquinavir) as a first line of treatment in patients with low CD4 cell counts.²⁴
- In the phase I/II study, 48 HIV-infected children (median age, 7.7 years; range, 0.5 to 14.4 years) were given either of the 4 dose levels of ritonavir oral solution (250, 300, 350, and 400 mg/m given every 12 hours) were evaluated in two age groups (≤ 2 years, > 2 years). Ritonavir was administered alone for the first 12 weeks and then in combination with zidovudine and/or didanosine. Clinical and laboratory parameters were monitored every 2 to 4 weeks. Ritonavir was well absorbed at all dose levels, and plasma concentrations reached a peak 2 to 4 hours after a dose. CD4 cell counts increased by a median of 79 cells/mm³ after 4 weeks of monotherapy and were maintained throughout the study. Plasma HIV RNA decreased by 1 to 2 log₁₀ copies/ml within 4 to 8 weeks of ritonavir monotherapy, and this level was sustained in patients enrolled at the highest dose level of 400 mg/m for the 24-week period.²⁵
- In a study, the effect of 12 weeks of treatment with zidovudine, lamivudine and ritonavir was studied on immune reconstitution in 44 persons with moderately advanced HIV-1 infection. After treatment, plasma HIV-1 RNA fell a median of 2.3 logs ($P < .0001$) while circulating numbers of naive and memory CD4 T lymphocytes ($P < .001$), naive CD8 T lymphocytes ($P < .004$), and B lymphocytes ($P < .001$) increased. Improved lymphocyte proliferation to certain antigens and a tendency to improvement in delayed-type hypersensitivity also were seen.²⁶
- In an international, multi-centric, randomized and placebo-controlled clinical trial, 1090 HIV-infected patients with CD4 cell counts $\leq 100 \times 10^6/l$ were randomized to ritonavir and continued treatment with as many as two nucleoside agents ($n=543$) or placebo and continued treatment with as many as two nucleoside agents ($n=547$). Health-related quality of life was measured at baseline and after 3 and 6 months of treatment using the Medical Outcomes Study HIV Health Survey (MOS-HIV) and HIV-related symptoms scale. The two treatment groups were comparable on baseline CD4 cell counts, demographic characteristics, and MOS-HIV and HIV symptom subscale scores. After 3 months, statistically significant differences ($P < 0.03$) favouring the ritonavir-treated patients were seen on the physical health summary, mental health summary, and general health perceptions, social function, mental health, and energy/fatigue subscales. After 6 months of ritonavir therapy, significant differences were observed on physical health and mental health summary scores ($P < 0.001$), and on measures of general health perceptions, physical function, role function, social function, cognitive function, mental health, health distress,

energy/fatigue, and overall ratings of quality of life ($P<0.01$). Ritonavir-treated patients reported fewer fever symptoms and neurologic symptoms than the placebo group after 6 months of treatment ($P<0.005$). Thus, ritonavir therapy, combined with other anti-retroviral treatments, significantly contributes to maintenance of functioning and well-being over at least 6 months in patients with advanced HIV disease.²⁷

- Current recommendations suggest that anti-retroviral therapy be considered in any patient with a viral load higher than 5,000 to 20,000 copies per ml, regardless of the CD4+ count. Selection of the combination regimen must take into account the patient's prior history of anti-retroviral use, the side effects of these agents and drug-drug interactions that occur among these agents and with other drugs as well. Because of the potential for viral resistance, nonnucleoside reverse transcriptase inhibitors and protease inhibitors should only be used in combination therapy. Anti-retroviral agents are rapidly being developed and approved, so physicians must make increasingly complex treatment decisions about medications with which they may be unfamiliar.²⁸
- An isolated case report published in 1998 has described complete clinical resolution of mucocutaneous Kaposi's sarcoma (KS) lesions with ritonavir therapy.²⁹

VIRAL RESISTANCE

Viral resistance has been observed after continuous use as a result of mutation of HIV protease, beginning at amino acid 82. Although the initial mutants were still sensitive to the drug, the secondary (involving 54, 71 and 36 amino acids) and tertiary (involving 20, 33, 46, 84 amino acids) mutants were progressively resistant to ritonavir. The results suggested that multiple mutations were required for the development of high level resistance.³⁰

The pattern of resistance between ritonavir and saquinavir is divergent, which is evident by the fact that mutations causing increased resistance to ritonavir also bestowed increased resistance to indinavir but not to saquinavir.³¹ Clinical isolates from 4 patients treated with indinavir for 1 year exhibited increased cross resistance to all protease inhibitors examined (Saquinavir, telonavir and VX-478).³² Moreover, mutations known to increase resistance to ritonavir were present in the clinical isolates from these patients.³²

DRUG INTERACTIONS

In vitro, ritonavir is a potent inhibitor of CYP3A metabolism (eg, clarithromycin, ketoconazole, rifabutin, and other HIV protease inhibitors, including indinavir, saquinavir and nelfinavir) with effects ranging from an increase of 77% to 20-fold in humans. It also inhibits CYP2D6-mediated metabolism, but to a significantly lesser extent (145% increase in desipramine AUC).^{33,34} Since ritonavir is also an inducer of several metabolizing enzymes [CYP1A4, glucuronosyl transferase (GT), and possibly

CYP2C9 and CYP2C19], the magnitude of drug interactions is difficult to predict, particularly for drugs that are metabolized by multiple enzymes or have low intrinsic clearance by CYP3A. For example, the AUC of CYP3A substrate methadone was slightly decreased and alprazolam was unaffected. Other CYP3A inhibitors minimally affect Ritonavir, including ketoconazole. Rifampicin (rifampin), a potent CYP3A inducer, decreased the AUC of ritonavir by only 35%. The degree and duration of suppression of HIV replication is significantly correlated with the plasma concentrations. Thus, the large increase in the plasma concentrations of other protease inhibitors when co-administered with ritonavir forms the basis of rational dual protease inhibitor regimens, providing patients with 2 potent drugs at significantly reduced doses and less frequent dosage intervals.⁵

Concomitant administration of ritonavir and ergotamine may result in severe ergotism.³⁵ No dose adjustments for ritonavir are presently recommended during concomitant fluoxetine administration. See *table 2 for details*.

Table II: Drugs likely to interact with Ritonavir are and therefore should be used with caution in conjunction with ritonavir are^{8,37-39}

Alprazolam	Amfebutamone	Amiodarone	Astemizole	Bepidil
Cisapride	Clorazepate	Clozapine	Diazepam	Encainide
Estazolam	Ergotamine	Flecainide	Flurazepam	Midazolam
Pethidine	Pimozide	Piroxicam	Piropafenone	Quinidine
Rifabutin	Terfenadine	Triazolam	Zolpidem	Dihydroergotamine
Quinine	Ketoconazole	Itraconazole	Loratidine	Dexamethasone
Methadone	Nefazadone	Sertraline		

Both in vitro and in vivo studies

- Ritonavir causes marked inhibition of the metabolism of other protease inhibitors in vitro preparations of rat and human liver microsomes. In rats, co-administration of ritonavir increases the AUC of saquinavir, nelfinavir, indinavir and VX478 by 36, 10, 8 and 8 folds respectively.⁴⁰
- In single and multi dose clinical trials in healthy volunteers, ritonavir increased the AUC and C_{max} of saquinavir.⁴¹ Studies with saquinavir (SQV) and small doses of ritonavir (RTV) suggest that single daily doses of saquinavir (1600 mg) may result in sufficient SQV serum levels throughout an interval of 24 h when given along with 200 mg ritonavir. However, due to high variability seen with all protease inhibitors it is recommended that continuous therapeutic drug monitoring of serum trough levels should be done.
- No clinical significant interactions were seen with didanosine, fluconazole or zidovudine when tested in patients

with HIV infections or healthy volunteers.⁴²⁻⁴⁴

ADVERSE DRUG REACTIONS

- Adverse events associated with ritonavir are generally reversible and tolerable.^{7,9} In a large double blind trial (n=1088), patients received either ritonavir (n=41) or placebo (n=547) in conjunction with their baseline anti-retroviral agents. Gastrointestinal and neurological adverse events of possible or unknown relationships were most frequently reported after 2.4 months of treatment.⁸
- There were 17% and 6% withdrawal from treatment due to adverse reactions receiving ritonavir (600 mg/day) or placebo respectively.¹¹ However, most withdrawals occurred in the period of drug initiation. The withdrawal rate in patients who continued receiving ritonavir was similar to the rate in placebo recipient's.¹⁵
- Laboratory abnormalities associated with ritonavir therapy included asymptomatic elevation of triglycerides and hepatic transaminase.⁷⁻⁹ Although a causal relationship was not established, ritonavir when given to approximately 15 patients in Europe with haemophilia receiving HIV protease inhibitors including ritonavir were associated with the same spontaneous bleeding events.⁴⁵
- Acute pancreatitis has been reported as a complication of ritonavir therapy in a patient with AIDS.⁴⁶

- Ritonavir has been reported to cause acute renal failure in 8 patients after 3-21 days of therapy.^{47,48}

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