Protease inhibitors: promising new weapons against HIV

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PROTEASE INHIBITORS, the most potent agents active against human immunodeficiency virus (HIV) introduced to date, have proved capable of decreasing the number of circulating HIV RNA particles by a factor of 100 or more, raising CD4 lymphocyte counts by 300 to 500 cells per mm^3, and, in one study,[1] decreasing the mortality rate in HIV infection.

The three approved protease inhibitors—saquinavir, ritonavir, and indinavir—are reasonably tolerated and, with a mechanism of action different from that of reverse transcriptase inhibitors such as zidovudine, have a synergistic effect with them. The disadvantages of protease inhibitors are their limited bioavailability after oral administration, their many drug interactions, their cost ($360–660 per month), and the emergence of strains of HIV resistant to these agents.

Unresolved is how these drugs should be used. Most trials have been in patients with advanced HIV infection. The benefits of protease inhibitors also likely apply to persons with intermediate-stage disease, but clinical data are still pending. No data are currently available examining the protease inhibitors in early-stage disease. Any guideline will ultimately require further validation by clinical studies, which are currently in progress.

This brief review is intended to update internists on the use of these important new drugs for treating HIV infection, provide an overview of their adverse reactions, and summarize data from recent human trials.

MECHANISM OF ACTION

The protease inhibitors act late in the replicative cycle of HIV. After the immature virion has budded from the host cell, it is not infectious until one of its polyproteins (*gag-pol*) releases the protease enzyme, which cleaves the parent *gag-pol* polyprotein at multiple sites, allowing the virion to mature. Inhibition of the protease enzyme leaves the immature viral particle incapable of initiating infection.[2–6]

SAQUINAVIR

Saquinavir is the first protease inhibitor approved by the US Food and Drug Administration.

Adverse reactions

Saquinavir is generally well tolerated. Reported side effects have been mild and mainly consist of nausea and diarrhea. The incidence of peripheral neuropathy is low. Rare, serious adverse reactions possibly related to saquinavir include Stevens-Johnson syndrome, seizures, and ataxia. Saquinavir did not increase the toxicity of zalcitabine or zidovudine in studies of combination therapy. Anemia and thrombocytopenia are uncommon, although approximately 2% of patients had a decreased neutrophil count in available studies.[6–9]

Drug interactions

Saquinavir is metabolized rapidly into inactive compounds by the hepatic cytochrome P450 system. Medications such as phenytoin, phenobarbital, and

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carbamazepine that activate the cytochrome P450 system (specifically the isoenzyme CYP3A4) can reduce plasma concentrations of saquinavir considerably; saquinavir's manufacturer recommends using alternatives to these agents if possible. In addition, rifampin and rifabutin decrease saquinavir concentrations by 80% and 40%, respectively.

Saquinavir itself can inhibit the cytochrome P450 3A pathway, potentially leading to increased plasma concentrations of the antihistamines terfenadine (Seldane) and astemizole (Hismanal). Although saquinavir is not a potent inhibitor of this pathway and no adverse events have been reported, giving these drugs with saquinavir could possibly induce cardiac arrhythmias (prolonged QT interval). Other drugs that use the P450 3A pathway include quinidine, clindamycin, and calcium antagonists. These drugs are not contraindicated in patients receiving saquinavir, but monitoring for drug toxicity is recommended.

Bioavailability

The bioavailability of oral doses of saquinavir is improved by giving it within 2 hours of a full meal; however, even then the bioavailability may be as low as 4%. About 98% of the absorbed dose is protein-bound and is distributed in the tissues.[9]

Dosage and administration

Saquinavir is available as a 200-mg capsule and should be given at 600 mg three times a day within 2 hours of a meal (*Table 1*). To prevent the development of drug resistance, lower doses should be avoided. Pilot studies are underway using higher doses (7200 mg daily) and new formulations with enhanced oral bioavailability.

TABLE 1
CURRENTLY APPROVED PROTEASE INHIBITORS

Agent	Oral dosage
Saquinavir (Invirase)	600 mg three times a day (Give with a full meal)
Ritonavir (Norvir)	600 mg two times a day (Give with food)
Indinavir (Crixivan)	800 mg three times a day (Give with water > 1 hour before meal or > 2 hours after meal)

RITONAVIR

Ritonavir is the only protease inhibitor thus far shown to decrease the mortality rate in HIV infection.[1]

Adverse reactions

The most common adverse reactions are nausea, vomiting, general asthenia, and abdominal pain. In addition, neurologic abnormalities such as taste perversions, circumoral paresthesias, and peripheral paresthesias may be seen. Ritonavir seems to have little hematologic toxicity, but more than 2% of patients have elevated liver function enzymes and creatine kinase levels.[11–15]

Drug interactions

Ritonavir is metabolized mainly by the hepatic cytochrome P450 3A system. Drug interactions are particularly troublesome with ritonavir, which increases the plasma levels of many other drugs considerably. *Table 2* lists some of the drugs contraindicated during ritonavir therapy for this reason. Ritonavir may also increase the plasma levels of other protease inhibitors given simultaneously, but its own levels change little.[15] This effect is likely due to ritonavir's very potent inhibition of the cytochrome P450 system. Ritonavir is being examined in regimens using multiple protease inhibitors, to prevent resistance to saquinavir.

Bioavailability

The absolute bioavailability of ritonavir in humans is not known, but its relative absorption is improved by 15% when given with a meal.

Dosage and administration

Ritonavir is supplied as a 100-mg capsule and as a flavored oral solution (80 mg/mL). The recommended dosage is 600 mg twice daily, with food. Because some patients experience gastrointestinal upset when ritonavir is started at a full dose, the drug can be started at 300 mg twice a day for 2 days and then increased to 400 mg twice a day for 4 days, 500 mg twice a day for 8 days, and then 600 mg twice a day. Prolonged courses of ritonavir at low doses are likely to lead to drug resistance.

INDINAVIR

Indinavir is the most recently approved protease inhibitor.[6,17–20]

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TABLE 2
MEDICATIONS CONTRAINDICATED IN PERSONS RECEIVING RITONAVIR

Alprazolam (Xanax)	Flurazepam (Dalmane)
Amiodarone (Cordarone)	Meperidine (Demerol)
Astemizole (Hismanal)	Midazolam (Versed)
Bepridil (Vascor)	Piroxicam (Feldene)
Bupropion (Wellbutrin)	Propafenone (Rythmol)
Cisapride (Propulsid)	Propoxyphene (Darvon)
Clorazepate (Tranxene)	Quinidine
Clozapine (Clozaril)	Rifabutin (Mycobutin)
Diazepam (Valium)	Terfenadine (Seldane)
Encainide (Enkaid)	Triazolam (Halcion)
Estazolam (ProSom)	Zolpidem (Ambien)
Flecainide (Tambocor)	

TABLE 3
DRUG INTERACTIONS WITH INDINAVIR

Drug	How to decrease interaction
Didanosine (ddI, Videx)	Give at least 1 hour before or after indinavir, on an empty stomach
Ketoconazole (Nizoral)	Reduce indinavir dose to 600 mg by mouth every 8 hours
Rifabutin (Mycobutin)	Reduce rifabutin dose by 50%
Rifampin	Coadministration not recommended, because of decreased indinavir concentrations
Astemizole (Hismanal)	Contraindicated
Cisapride (Propulsid)	Contraindicated
Midazolam (Versed)	Contraindicated
Terfenadine (Seldane)	Contraindicated
Triazolam (Prosom)	Contraindicated

Adverse reactions

Indinavir is generally well tolerated, although nephrolithiasis occurred in 4% of patients in available studies and was sometimes accompanied by hematuria.[17] The episodes generally resolved with hydration. Asymptomatic hyperbilirubinemia (mostly involving the indirect bilirubin fraction) occurred in 10%. Other relatively common adverse reactions include abdominal pain, fatigue, nausea, vomiting, headache, dizziness, taste perversion, and flank pain.

Drug interactions

Indinavir's metabolism is similar to that of the other protease inhibitors. Important drug interactions are shown in *Table 3*.

Bioavailability

Unlike saquinavir and ritonavir, indinavir has decreased oral absorption if given with a meal high in fat and protein. However, a light meal or coffee does not substantially change its absorption.

Dosage and administration of indinavir

Indinavir is available as 200-mg and 400-mg capsules. The recommended dosage is 800 mg every 8 hours, with or without other antiretroviral agents. It should be given 1 hour before or 2 hours after a meal, but can be given with toast, coffee, juice, or cereal with skim milk. In hepatic dysfunction the dosage should be decreased to 600 mg every 8 hours. The pharmacokinetics of indinavir in renal failure are unknown.

VIRAL RESISTANCE TO PROTEASE INHIBITORS

The emergence of resistance may be a major reason for drug failure. Resistance to saquinavir developed in vitro and in approximately 45% of patients who received it as monotherapy for 1 year,[6,10] and resistance to ritonavir[11] and indinavir has also been noted. Cross-resistance between the protease inhibitors is a complex but clinically important issue. One concern is that resistance that develops while on therapy with a specific protease inhibitor may also induce resistance to multiple protease inhibitors.[18] However, different mutations in the HIV protease gene account for resistance to saquinavir compared with resistance to the other two agents.[12] Further, in one study, prolonged treatment with saquinavir did not lead to cross-resistance to other protease inhibitors.[10] Although cross-resistance is uncommon between indinavir and reverse transcriptase inhibitors, it can occur between indinavir and ritonavir.[6,17,18] The incidence and clinical significance of cross-resistance are still under study and emphasize the need to use the most potent protease inhibitor available and to encourage full compliance with the complex dosing schemes in all patients.

THE AUTHOR'S PERSPECTIVE

The improvements in CD4 lymphocyte count and viral load demonstrated with the protease in-

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Protease inhibitors in human trials

To date, all but one trial of protease inhibitors have reported their effects on surrogate markers only—ie, on HIV RNA levels ("viral load") and CD4 lymphocyte counts—and not on clinical endpoints such as mortality rates. Although the significance of viral load is still under study, there is mounting evidence that it accurately and independently predicts disease progression.[1,2] Further, preliminary analysis from the one clinical trial that did examine mortality rates did show a clinical benefit with the use of the protease inhibitor ritonavir.[3]

Trials with saquinavir

Saquinavir appears more effective when used in combination with zidovudine (in persons who have not previously received zidovudine, in whom the combination increased the CD4 count by 70% and decreased the HIV RNA level by 97% [1.5 log] in one study) or with zalcitabine (in persons who have received zidovudine, in whom a combination of saquinivir, ziduvidine, and zalcitabine increased the HIV RNA level by 68% [0.5 log] in another study). However, HIV RNA levels and CD4 counts tended to return to baseline values after 24 weeks in these studies.[4]

Trials with ritonavir

Ritonavir was found more effective than placebo in two phase 2 studies.[5,6] In another, ongoing study in patients who had not previously received antiretroviral drugs, an interim analysis showed that ritonavir raised the CD4 cell count by a mean of 62 cells per μL, compared with 10.7 cells per μL in those receiving zidovudine alone. The viral RNA level decreased by 91% (1.03 log) in the group receiving ritonavir alone, vs 62% (0.42 log) in the zidovudine group.[7] In a trial in patients with advanced infection who had received at least 9 months of previous antiretroviral therapy (and who continued to take their previous antiretroviral drugs throughout the trial), the cumulative mortality rate at 6 months was lower in patients receiving ritonavir 600 mg twice a day than in those receiving placebo (5.5% vs 10.1%). An AIDS-defining clinical event or death occurred in 17% of those receiving ritonavir vs 34% receiving placebo.

Trials with indinavir

In an ongoing study in patients without previous antiretroviral therapy, a combination of indinavir plus zidovudine led to a mean reduction in HIV RNA of 91% (1.04 log), compared with 44% (0.25 log) with zidovudine alone. The CD4 cell count increased by a mean of 95 cells per mm^3 in the combination therapy group, compared with 13.7 cells per mm^3 in the zidovudine-alone group.[8] In another study, patients who had previously received zidovudine had a 98% (1.77 log) decrease in HIV RNA with combination therapy with indinavir, zidovudine, and lamivudine, compared with 78% (0.67 log) with zidovudine and lamivudine.[9] The CD4 cell count increased by 100 cells per mm^3 in the triple drug combination group vs an increase of 33 cells per mm^3 in those receiving zidovudine and lamivudine. Clinical outcome data are forthcoming.

References

1. **Mellors JW, Kingsley LA, Rinaldo CR Jr, et al.** Quantitation of HIV RNA in plasma predicts outcome after seroconversion. Ann Intern Med 1995; **274:**554–558.
2. **Havlir DV, Richman DD.** Viral dynamics of HIV: implications for drug development and therapeutic strategies. Ann Intern Med 1996; **124:**984–994.
3. **Cameron B, Heath-Chiozzi M, Kravcik S, et al.** Prolongation of life and prevention of AIDS in advanced HIV immunodeficiency with ritonavir [abstract]. In: Program and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C., January 29–February 1, 1996. Washington, D.C.: American Society of Microbiology, 1996.
4. **Schapiro JM, Winters MA, Merigan TC.** First efficacy and safety results of the high dose saquinavir monotherapy trials [abstract]. In: Program and abstracts of the Second National Conference on Human Retroviruses and Related Infections, Washington, D.C., January 29–February 2, 1995: American Society of Microbiology, 1995, abstract LB2.
5. **Markowitz M, Saag M, Powderly WG, et al.** A preliminary study of ritonavir, an inhibitor of HIV-1 protease, to treat HIV-1 infection. N Engl J Med 1995; **333:**1534–1539.
6. **Danner SV, Carr A, Leonard JM, et al.** A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. N Engl J Med 1995; **333:**1528–1533.
7. Norvir product information. Abbott Laboratories, North Chicago, IL, February 1996.
8. Crixivan product information. Merck & Co., Inc. West Point, PA. March 1996.
9. **Gulick R, Mellors J, Havlir D, Erlon J, Gonzalez C.** Potent and sustained antiretroviral activity of indinavir in combination with zidovudine and lamivudine [abstract]. In: Program and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C., January 29–February 1, 1996. Washington, D.C.: American Society of Microbiology, 1996.

hibitors are unprecedented. Ritonavir and indinavir have the most favorable pharmacokinetic profiles and appear to be the more potent of the available protease inhibitors; other protease inhibitors are under development. Clinical trials have focused mainly on HIV-infected persons with advanced disease but benefit has also been shown with intermediate-stage HIV infection. The drugs are generally well tolerated, but the complexities of the drug interactions and the number of pills required (6 to 12

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per day) are important issues for the clinician.

The optimal strategy for the protease inhibitors is still evolving, and considerable practice variation exists. One approach would be to use a protease inhibitor as part of a multidrug regimen (eg, zidovudine, lamivudine, and ritonavir) in patients with fewer than 100 CD4 cells per mm^3, based on the recent clinical trial that showed clinical benefits in addition to improvements in laboratory markers. The role of protease inhibitors in patients with intermediate-stage disease (ie, a CD4 count between 100 and 500 cells per mm^3) is more problematic. A protease inhibitor could be added to a nucleoside analog regimen if there is clinical evidence of rapid disease progression or persistently elevated HIV RNA levels during nucleoside analogue therapy. This strategy is based in part on clinical trial designs but requires further validation; the cut-point for an elevated HIV RNA level is also unknown. Because of the favorable risk/benefit ratio of these drugs, we have been offering protease inhibitors to many of our patients with late-stage disease and selected patients with intermediate-stage disease.

REFERENCES

1. **Cameron B, Heath-Chiozzi M, Kravcik S, et al.** Prolongation of life and prevention of AIDS in advanced HIV immunodeficiency with ritonavir [abstract]. In: Program and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C., January 29–February 1, 1996. Washington, D.C.: American Society of Microbiology, 1996.
2. **Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M.** Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995; **373:**123–126.
3. **Wei X, Ghosh SK, Taylor ME, et al.** Viral dynamics in human immunodeficiency virus type 1 infection. Nature 1995; **373:**117–122.
4. **Kohl NE, Emini EA, Schleif WA, et al.** Active human immunodeficiency virus protease is required for viral infectivity. Proc Natl Acad Sci USA 1988; **85:**4686–4690.
5. **Debouck C.** The HIV-1 protease as a therapeutic target for AIDS. AIDS Res Hum Retroviruses 1992; **8:**153–164.
6. **Vella S.** Update on HIV protease inhibitors. AIDS Clinical Care 1995; **7(10):**79–82,88.
7. **Kitchen VS, Skinner C, Ariyoshi K, et al.** Safety and activity of saquinavir in HIV infection. Lancet 1995; **345:**952–955.
8. **Schapiro JM, Winters MA, Merigan TC.** First efficacy and safety results of the high dose saquinavir monotherapy trials [abstract]. In: Program and abstracts of the Second National Conference on Human Retroviruses and Related Infections, Washington, D.C., January 29–February 2, 1995: American Society of Microbiology, 1995, abstract LB2.
9. Invirase product information. Hoffman-La Roche Inc., Nutley, NJ, December 1995.
10. **Duncan IB, Jacobsen H, Owen S, Robers NA.** Reduced HIV sensitivity during treatment with the proteinase inhibitor saquinavir [abstract]. In: Program and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C, January 29–February 1, 1996. washington, D.C.: American Society of Microbiology, 1996.
11. Norvir product information. Abbott Laboratories, North Chicago, IL, February 1996.
12. **Eastman PS, Kelso R, Boyer E, et al.** Loss of suppression of viral replication by ritonavir (ABT-538) is quantatively associated with acquisition of genotypic mutations at codon 82 of the HIV-1 protease gene. In: Programs and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C., January 29–February 1, 1996. Washington, D.C.: American Society of Microbiology, 1996.
13. **Markowitz M, Saag M, Powderly WG, et al.** A preliminary study of ritonavir, an inhibitor of HIV-1 protease, to treat HIV-1 infection. N Engl J Med 1995; **333:**1534–1539.
14. **Danner SV, Carr A, Leonard JM, et al.** A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. N Engl J Med 1995; **333:**1528–1533.
15. **Kempf D, Marsh K, Denissen J, et al.** Coadministration with ritonavir enhances the plasma levels of HIV protease inhibitors by inhibition of cytochrome P450 [abstract]. In: Program and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C., January 29–February 1, 1996. Washington, D.C.: American Society of Microbiology, 1996.
16. **Kelleher AD, Carr A, Zaunders J, Cooper DA.** Alterations in the immune response of human immunodeficiency virus (HIV)-infected subjects treated with an HIV-specific protease inhibitor, ritonavir. J Infect Dis 1996; **173:**321–329.
17. Crixivan product information. Merck & Co., Inc. West Point, PA. March 1996.
18. **Condra JH, Schleif WA, Blahy OM, et al.** In vivo evolution of resistance to the HIV-1 protease inhibitor indinavir [abstract]. In: Program and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C., January 29–February 1, 1996. Washington, D.C.: American Society of Microbiology, 1996.
19. **Gulick R, Mellors J, Havlir D, Erlon J, Gonzalez C.** Potent and sustained antiretroviral activity of indinavir in combination with zidovudine and lamivudine [abstract]. In: Program and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C., January 29–February 1, 1996. Washington, D.C.: American Society of Microbiology, 1996.
20. **Steigbigel RT, Berry P, Mellors J, et al.** Efficacy and safety of the HIV protease inhibitor indinavir sulfate (MK 639 at escalating doses [abstract]. In: Program and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C., January 29–February 1, 1996. Washington, D.C.: American Society of Microbiology, 1996.
21. **Massari F, Conant M, Mellors J, et al.** A phase II open-label, randomized study of the triple combination of indinavir, zidovudine (ZDV), and didanosine (DDI) versus indinavir alone and zidovudine/didanosine in antiretroviral naive patients [abstract]. In: Program and abstracts of the Third National Conference on Human Retroviruses and Related Infections. Washington, D.C., January 29–February 1, 1996. Washington, D.C.: American Society of Microbiology, 1996.
22. **Mellors JW, Kingsley LA, Rinaldo CR Jr, et al.** Quantitation of HIV RNA in plasma predicts outcome after seroconversion. Ann Intern Med 1995; **274:**554–558.
23. **Havlir DV, Richman DD.** Viral dynamics of HIV: implications for drug development and therapeutic strategies. Ann Intern Med 1996; **124:**984–994.

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