



Pharmacy Update

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Nelfinavir (Viracept®): A Brief Review

Introduction

Nelfinavir is the fourth protease inhibitor of human immunodeficiency virus type 1 (HIV-1) approved for the treatment of HIV infection. It is the first protease inhibitor approved for use in pediatric patients (over 2 years of age). The approval of this agent, as with other protease inhibitors, is primarily based on surrogate markers of immunological (CD4 cell count) and virological (viral burden) response to therapy, when used in combination with nucleoside reverse transcriptase inhibitors (NRTIs). At the time of drug approval, surrogate marker response data for up to 24 weeks of therapy were available. Extended experience for up to 10 months was recently reported and demonstrated similar results. No long-term efficacy data on disease progression and survival are available to date.

Description

Viracept® (nelfinavir mesylate) is available as 250 mg tablets and as an oral powder preparation.

Indications

Nelfinavir is approved by the FDA for the treatment of HIV infection when anti-retroviral therapy is warranted. It should always be used in combination with at least one other anti-retroviral agent.

Pharmacology

Mechanism of Action: Nelfinavir is an inhibitor of HIV-1 protease, which results in preventing cleavage of the gag-pol polyprotein. This leads to production and release of immature, non-infectious virions, thus inhibiting viral replication. Nelfinavir has demonstrated in vitro activities against various laboratory and clinical isolates of HIV-1 and HIV-2.

Effects of Combination Therapy with Other Anti-Retroviral Agents:

When combined with NRTIs in vitro, nelfinavir was found to be synergistic with zidovudine (ZDV), lamivudine (3TC), and zalcitabine (ddC) against HIV-1. It is at least additive, if not synergistic, with didanosine (ddI) and stavudine (d4T). Antiviral activities, when combined with other protease

inhibitors, have shown variable results ranging from antagonistic to synergistic. Clinical significance of these in vitro data is not yet known. Antiviral effects of nelfinavir, when combined with non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine or delavirdine, have not been reported.

Drug Resistance: Development of decreased viral susceptibility to nelfinavir has been shown in patients treated with nelfinavir as monotherapy or in combination with NRTIs. At least one mutation at various amino acid positions has been detected in more than 10% of patients with evaluable HIV isolates. The most common mutation site is found at position 30 of the protease gene. The incidence of phenotypic resistance at this site is much higher in patients receiving nelfinavir monotherapy than in those receiving combination therapy with ZDV and 3TC (55% vs 6%, respectively).

Cross Resistance with Other Protease Inhibitors: When isolates with significantly reduced susceptibility to nelfinavir are tested in vitro with ritonavir, indinavir, or saquinavir, they remain susceptible to these three protease inhibitors. However, when clinical isolates resistant to ritonavir were tested for susceptibility to nelfinavir, six of seven isolates also demonstrated resistance to nelfinavir in vitro. These results suggest that patients who develop resistance to nelfinavir can potentially be successfully treated with the other protease inhibitors. Due to differences in the mechanism of action of the NRTIs, cross resistance between nelfinavir and these agents is not expected.

Pharmacokinetics

Mechanism of Action: Oral Absorption: After oral administration of nelfinavir (500 to 750 mg with food), peak plasma concentrations are generally achieved between two and four hours. Both the peak plasma concentration and area under the curve (AUC) are approximately two- to three-fold higher when the doses are taken under a fed versus fasting condition.

Drug Distribution and Protein Binding: The estimated volume of distribution of nelfinavir (2-7 L/kg) exceeds that of total body water, suggesting distribution to tissue compartments. A single dose study in rats showed that brain concentrations exceeded the EC95 against HIV-1; no human data are available to date. Nelfinavir is > 98% bound to protein in serum.

Metabolism: Nelfinavir can be metabolized via the cytochrome P450 system, with isoform CYP3A4 responsible for majority of its metabolism. One major metabolite has been identified in the plasma which possesses antiviral activity similar to that of the parent compound.

Elimination: The majority of a dose of nelfinavir (consisting of oxidative metabolites and unchanged drug) is recovered in the feces. Only 1-2% of

the drug is recovered in the urine.

Pharmacokinetics in Children: Preliminary reports from a Phase I study in pediatric patients led to the current dosage recommendations for children. The children were divided into two groups-ages 2 to 7 years and 7 to 13 years. At 10 mg/kg, both groups achieved AUCs of approximately 20-40% of the weight-adjusted dose in adults. At 30 mg/kg, the 2 to 7 year old group achieved 150% the AUC of adults. Nelfinavir clearance in children is two- to three-fold higher than in adults on a weight-adjusted basis. Based on this information, the current pediatric dosage is approximately 20-30 mg/kg per dose.

Selected Clinical Studies

To date, three Phase II/III double-blind, randomized, controlled trials have been conducted with nelfinavir as monotherapy or combination therapy. Below are a summary of the results from some of these studies, as well as those from some smaller studies.

1. [Nelfinavir (NFV) 500 mg TID + Zidovudine (ZDV) + Lamivudine (3TC)] vs [Nelfinavir 750 mg TID + ZDV + 3TC] vs [ZDV + 3TC]

This three arm study compared two doses of nelfinavir in combination with ZDV + 3TC versus ZDV + 3TC without a protease inhibitor. Patients studied had less than one month of ZDV therapy and had no other prior antiretroviral therapy (ART). There was no restriction in baseline CD4 cell count. A total of 297 patients were enrolled in this study. Median CD4 cell count at entry for all patients was 288 cells/mm³ and mean viral RNA was 153,044 copies/mL. Both doses of NFV plus ZDV and 3TC resulted in significantly greater decreases in viral load than in the ZDV + 3TC group (p=0.0001). At 24 weeks, the following viral load and CD4 cell count responses were reported:

	3TC + ZDV + NFV 750	3TC + ZDV + NFV 500	3TC + ZDV
% HIV RNA Decrease	88%	75%	36%
Mean CD4 Count Increase (cells/mm ³)	146	138	95

A follow-up of this study was recently presented at the 10th International Conference on Antiviral Research. After 10 months, 87% of the patients randomized to the NFV 750 mg + ZDV + 3TC arm had viral RNA that remained undetectable, with a mean CD4 count increase of 173 cells/mm³. Among 12 advanced patients who had CD4 counts < 50 cells/mm³ at study

entry, who received the 750 mg dose of nelfinavir, the mean reduction of plasma HIV RNA was 2.2 log, with 11 of the 12 patients having undetectable viral loads at 10 months.

Markowitz and colleague reported similar experiences in 12 ART-naive patients receiving this drug combination (using nelfinavir 750 mg TID). At 16 weeks, the mean HIV RNA decreased by 3.9 log. Eight of 10 patients had undetectable viral loads and negative HIV cultures at 52 weeks. In addition, eight of nine patients had HIV below quantifiable levels in lymphoid tissue after 11-15 months of therapy.

These two studies report the longest follow-up experience thus far with nelfinavir and two NRTI combinations, demonstrating successful viral suppression at ten to fifteen months.

2. [NFV 500 mg TID + Stavudine (d4T) BID] vs [NFV 750 mg TID + d4T BID] vs [d4T BID]

This study evaluated the two doses of nelfinavir in combination with d4T vs d4T monotherapy. Patients had entry CD4 cell counts greater than or equal to 50 cells/mm³ and HIV RNA greater than or equal to 15,000 copies/mL. 308 patients were enrolled, 61 of whom were ART-naive and 247 of whom were ART-experienced. The mean duration of prior ART was 32 months. Mean baseline CD4 count was 279 cells/mm³ and mean baseline HIV RNA was 141,369 copies/mL. Patients were allowed to be switched to another arm or other treatment based on surrogate marker data or drug toxicities. Both doses of nelfinavir in combination with d4T produced a more significant decrease in viral load and increase in CD4 cell count ($p < 0.0001$) than d4T monotherapy. At the end of 24 weeks, 20%, 19%, and 2% of the nelfinavir 500 mg, 750 mg, and the d4T mono-therapy groups, respectively, had undetectable viral loads.

3. Open Label Study of Nelfinavir + Stavudine (d4T) + Didanosine (ddI)

An ongoing open-label pilot study is being conducted to evaluate the safety and virological efficacy of the combination of nelfinavir with d4T and ddI in patients who were naive to these three agents. All patients had HIV RNA greater than or equal to 10,000 copies/mL at study entry. Of 22 patients enrolled in the study, 11 had prior ART and 11 were ART-naive. The median CD4 cell count was 315 (range 70-709) and median HIV RNA was 4.75 log (range 4.00-5.58 log). The virological responses and CD4 count responses at weeks 2, 4, and 8 are as follows:

	Wk 2 (n=22)	Wk 4 (n=17)	Wk 8 (n=8)
Median CD4 change	+ 75	+ 103	+ 208

(cells/mm³)
Median HIV RNA change -1.4 log -1.7 log -2.1 log

At week 8, three of the eight remaining patients had HIV RNA < 500 copies/mL. The drug combination was well tolerated, with 17 patients reporting occasional loose bowel movements. A pharmacokinetic study was performed in patients taking nelfinavir with or without ddI. No pharmacokinetic interaction was observed between these two agents.

4. Phase I Study in Pediatric Patients

To date, only one phase I study has been conducted to assess the safety, single- and multiple-dose pharmacokinetics, and anti-viral activity of nelfinavir oral powder in children. Studies in the 0-3 month and 3 month to 2 year age groups are ongoing, and no data have been reported thus far. No definitive virological and immunological results are available to date in this population.

Adverse Effects

Nelfinavir is generally well tolerated. The most frequent adverse reaction is mild to moderate diarrhea, occurring in up to 32% of patients. Other reported reactions include flatulence, nausea, and skin rash. No significant laboratory abnormalities have been reported to date.

Drug Interactions

Nelfinavir, like other protease inhibitors, is an inhibitor of cytochrome P450 3A (CYP3A). Its effect on other drugs metabolized by CYP3A is not as pronounced as that of ritonavir, and is similar to that of indinavir. Coadministration with other drugs metabolized by this same pathway may result in increased plasma concentrations of the other agents. Since nelfinavir is partially metabolized by CYP3A, inducers of CYP3A coadministered with nelfinavir may decrease its plasma concentration. Conversely, coadministration with CYP3A inhibitors may increase nelfinavir concentrations.

The manufacturer recommends that the following medications not be coadministered with nelfinavir based on potentially significant drug-drug interactions that may lead to serious or life-threatening reactions: astemizole, terfenadine, rifampin, midazolam, triazolam, and cisapride. These are all theoretical contraindications; no significant reactions have actually been reported to date. The manufacturer suggests a dose reduction of rifabutin when coadministered with nelfinavir.

Other potential drug-drug interactions that should be considered include: anticonvulsants such as phenytoin, phenobarbital, or carbamazepine (which may decrease nelfinavir levels); protease inhibitors such as ritonavir or

indinavir (which may increase nelfinavir concentrations); and oral contraceptives (whose levels may be decreased by nelfinavir).

The pharmacokinetics of nelfinavir in combination with other marketed protease inhibitors have been studied. Nelfinavir has been shown to increase single dose exposure of the soft gel capsule formulation of saquinavir five-fold, which can be a positive interaction since saquinavir is poorly bioavailable as a single agent. Saquinavir does not appear to have any significant effect on the pharmacokinetics of nelfinavir. When the indinavir and nelfinavir combination was studied, the two drugs showed a bidirectional increase in AUC, with indinavir increasing the AUC of single dose nelfinavir by 184%, and nelfinavir increasing indinavir AUC by 150%.

Dosage and Administration

Adult Dosing: The current recommended dose for adults is 750 mg (three 250 mg tablets) taken with a meal or light snack three times daily. Dosage adjustment is not necessary in patients with renal dysfunction. Since nelfinavir is primarily metabolized in the liver, it should be used with caution in patients with hepatic dysfunction. Nelfinavir should be used in combination with other antiretroviral agents to enhance its antiviral activity.

Pediatric Dosing (2 to 13 years): The recommended dose in this age group is 20-30 mg/kg/dose three times daily with a meal or light snack. If the oral powder form is used, it can be mixed with a small amount of water, milk, formula, soy formula, soy milk, or dietary supplements. Once mixed, the entire contents should be consumed within six hours.

Cost

The monthly costs of adult doses of currently marketed protease inhibitors at NIH are as follows:

Drug	Daily Adult Dose	Cost Per Month
Nelfinavir (Viracept®)	750 mg q8h	\$ 470.44
Indinavir (Crixivan®)	800 mg q8h	\$ 268.99
Ritonavir (Norvir®)	600 mg q12h	\$ 748.64
Saquinavir (Invirase®)	600 mg q8h	\$ 358.45

Conclusion

Nelfinavir is the fourth protease inhibitor marketed for the treatment of

HIV infection. Based on clinical studies with one or two other nucleoside analogs for up to ten months, patients receiving nelfinavir-containing combinations have been able to maintain a more sustained viral load reduction and increase of CD4 cell count, when compared to using nucleoside analogs alone. As is true with other protease inhibitors, clinical endpoint results with nelfinavir are not yet available.

Nelfinavir has a unique resistance profile wherein patients with HIV strains that developed resistance to nelfinavir may still maintain susceptibility to other available protease inhibitors. Nelfinavir may theoretically be used as the first protease inhibitor for some patients, reserving other agents for later use.

Nelfinavir has been approved for pediatric patients. However, its immunological and virological efficacy in this population is still unknown. More studies in this age group will be essential to define its role in the management of HIV infection in children, particularly in those under 2 years of age.

To date, there are no data from comparative trials between nelfinavir and other protease inhibitors, when used with NRTIs. Clinical trials are either underway or are being planned. Since reported studies with all marketed protease inhibitors enrolled different patient populations, used various combinations of concomitant NRTIs, and utilized different viral load assays for determining virological responses, it is not possible to directly compare the results from these studies. Thus, the relative clinical, immunologic, and virologic potencies of all these agents are not yet known. Selection of which protease inhibitor(s) is (are) most appropriate for an individual patient should be based on the patient's prior experience with protease inhibitors, history of drug tolerance, potential drug-drug interactions, and dosing convenience.

References available upon request

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary actions:

Additions

- Nelfinavir (Viracept®), a protease inhibitor approved for the treatment of HIV infection
- Donepezil (Aricept®), a centrally acting cholinesterase inhibitor approved for use in the treatment of mild to moderate Alzheimer's disease
- Tizanidine (Zanaflex®), a centrally acting alpha-2 adrenoreceptor

agonist indicated for the acute and intermittent management of increased muscle tone associated with spasticity

- Ivermectin (Stromectol®), a broad-spectrum antihelmintic
- Atorvastatin (Lipitor®), a lipid-lowering HMG-CoA reductase inhibitor

Deletions

None

Editor's Note

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