Tipranavir: A Protease Inhibitor for HIV Salvage Therapy

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OBJECTIVE: To review the efficacy, safety, pharmacology, virology, pharmacokinetics, and resistance of the nonpeptidic protease inhibitor (PI) tipranavir.

DATA SOURCES AND STUDY SELECTION: A PubMed search (1966–February 2006) was conducted using the key words tipranavir or PNU-140690, with the limitation of English-language reports. Pharmacokinetic and randomized clinical trials originating from major HIV conferences, such as the Conference on Retroviruses and Opportunistic Infections, International AIDS Society, European AIDS Conference, and Interscience Conference on Antimicrobial Agents and Chemotherapy, published only in abstract form, from 2000 to February 2006, were reviewed for relevance and included in this review.

DATA SYNTHESIS: Phase III studies have shown that tipranavir is effective in the treatment of PI-resistant HIV compared with other PI-containing regimens. Adverse effects associated with tipranavir/ritonavir therapy include gastrointestinal reactions, hepatotoxicity, and elevations in cholesterol and triglyceride levels. Resistance data suggest that tipranavir/ritonavir should be reserved for salvage therapy in antiretroviral-experienced patients who have previously failed standard PI therapies. The potential for hepatotoxicity and drug interactions and the expense of tipranavir due to required ritonavir boosting may limit its widespread use.

CONCLUSIONS: Tipranavir/ritonavir is an essential addition to the antiretroviral armamentarium for HIV-infected patients with limited treatment options.

KEY WORDS: antiretroviral, HIV, protease inhibitor, tipranavir.

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Although protease inhibitors (PIs) have been shown to decrease morbidity and mortality in the treatment of HIV, the increasing risk of resistance among treatment-experienced and, more recently, treatment-naïve individuals, threatens the antiviral activity of this potent class of agents and limits the efficacy of highly active antiretroviral therapy.[1-3]

In response, researchers and pharmaceutical companies continue to focus their efforts on the creation of new antiretroviral agents (ARVs) with novel mechanisms of action and on improving preexisting ARVs. In June 2005, a new protease inhibitor, tipranavir, was approved by the Food and Drug Administration (FDA) for use in combination with ritonavir (TPV/r) for treatment-experienced HIV-positive individuals harboring PI-resistant virus. Tipranavir is manufactured in the US by Boehringer Ingelheim under the trade name Aptivus.[4]

Author information provided at the end of the text.

Data Sources

To identify relevant journal articles, a PubMed search was conducted (1966–February 2006) using the key words tipranavir or PNU-140690, with studies limited to those published in English. Reports of pharmacokinetic and randomized trials presented at major HIV conferences, such

as the Conference on Retroviruses and Opportunistic Infections, International AIDS Society, European AIDS Conference, and Interscience Conference on Antimicrobial Agents and Chemotherapy, and published only in abstract form, were also reviewed for relevance and included in this review. Data from the product monograph were also evaluated.

Pharmacology

Tipranavir is an HIV-1 PI that was discovered via iterative structure-based design. It has a novel, nonpeptidic structure that theoretically allows flexibility and close binding to the protease active site, even in the face of resistance mutations. Like other PIs, tipranavir interferes with HIV viral processing of essential gag and gag-pol proteins, resulting in the release of immature, noninfectious HIV virions.[5]

Virology

Tipranavir is a potent inhibitor of both HIV-1 and HIV-2 protease with enzyme inhibition constant values of 8 pM and less than 1 nM, respectively, in vitro.[6] For H9 cells and peripheral blood monocyte cells infected with laboratory strains of HIV-1, the 90% inhibitory concentration (IC_{90}) values were 0.16 μM.[7] In peripheral blood monocyte cells infected with HIV-1, the IC_{90} value was 0.18 μM. In peripheral blood monocyte cells infected with 10 different patient HIV viral isolates, the mean IC_{90} ± SD was 0.16 ± 0.07 μM.

PIs are susceptible to fold changes in activity due to plasma protein binding. The antiviral activity of tipranavir decreases approximately 3.75-fold in the presence of human serum.[4] An in vitro study with 10% fetal bovine serum and 75% human plasma of tipranavir in cells infected with the $HIV\text{-}1_{IIIB}$ laboratory strain determined the IC_{90} to be 1.4 μM.[6] The addition of 33% human plasma to tipranavir resulted in a 1.7-fold change in activity, while addition of 2 mg/mL of α-1 acid glycoprotein resulted in a 6.2-fold change in activity.[7] Although the fold change in tipranavir activity increased, the corresponding IC_{90} values did not exceed 2.1 μM.

Pharmacokinetics

The absorption of tipranavir is limited, but unquantified. A high-fat meal of 868 kcal enhances its absorption. In population pharmacokinetic studies, factors such as weight, gender, and HIV serostatus affected steady-state concentrations but did not warrant dosage adjustments.[8] In HIV-negative male and female volunteers taking tipranavir 500 mg with ritonavir 200 mg daily for longer than 2 weeks, the tipranavir maximum concentration of 61–117.6 μM was achieved in approximately 3 hours. The 12 hour AUC ranged from 503 to 1160 μM • hour. TPV's volume of distribution is 7.7 L for males and 10.2 L for females, with corresponding clearance values of 1.15 L/h for males and 1.27 L/h for females. Its half-life is 5.5 and 6 hours for males and females, respectively. Tipranavir is more than 99% protein bound by α-1 acid glycoprotein and serum albumin.[4]

To achieve adequate plasma concentrations, tipranavir 500 mg (two 250 mg capsules) must be coadministered with ritonavir 200 mg (two 100 mg capsules) twice daily. A dose-ranging study in treatment-naïve patients found that ritonavir increased tipranavir exposure by 24- to 70-fold.[9] This magnitude of boosting is required because tipranavir is both a substrate and potent inducer of P-glycoprotein and may initially induce its own metabolism.[4] The addition of ritonavir results in a net inhibition of CYP3A4 as estimated by erythromycin breath test and P-glycoprotein induction.[4,10] Tipranavir also inhibits CYP1A2, 2C9, and 2D6; however, the effects of ritonavir on these enzyme families are unknown.

Tipranavir is excreted primarily in feces as the unchanged drug (82%) and only minimally in urine (4%).[11] Major metabolites include 2 hydroxylated species in feces and a glucuronide conjugate in urine. Because very little tipranavir is excreted in urine, no dosage adjustments are necessary in patients with renal dysfunction.[4] HIV-negative volunteers with mild hepatic impairment (Child–Pugh score A, or <6) who were given TPV/r had nonsignificant increases in geometric mean ratios of tipranavir steady-state AUC and maximum concentration compared with matched controls, suggesting that no dosage adjustment is required in patients with mild hepatic dysfunction.[12] Further study is warranted for patients with moderate or severe hepatic impairment, and tipranavir is currently contraindicated for use in this population.[4]

Clinical Studies

PHASE II

Initially, tipranavir was developed as a hard-fill capsule, but the soft-gel formulation with double the bioavailability and lower pill burden entered Phase II and III trials and is the current FDA-approved formulation.[9] The results of the Phase II clinical studies are summarized in Table 1.[9,13-17]

In the BI 1182.3 study, it was demonstrated that ritonavir boosting of tipranavir 300 or 1200 mg twice daily provided significant viral load (VL) reductions compared with unboosted 1200 mg ($p < 0.05$).[9] At day 15, median VL reductions of greater than 1.5 $\log_{10}$ copies/mL were achieved by 40% of patients in the boosted 300 mg arm and 82% of those in the boosted 1200 mg arm compared with 0% in the unboosted arm. Changes in CD4+ cell counts between the groups were not significant.

In BI 1182.2, 41 subjects with detectable virus who had failed 2 or more PI-based regimens were randomized to receive TPV/r 1200/100 mg twice daily or 2400/200 mg

twice daily plus efavirenz 600 mg and 2 nucleoside reverse transcriptase inhibitors (NRTIs) initially.[13,14] During the study, subjects were switched from a hard-fill to the soft-gel tipranavir formulation at doses of 500 or 1000 mg boosted with ritonavir 100 mg twice daily. At 24 weeks, 77.8% of patients receiving TPV/r 500/100 mg had HIV RNA less than 400 copies/mL compared with 50% of those on the higher TPV/r dose (p = 0.10); 61.1% had a VL less than 50 copies/mL versus 50% of those on the higher dose (p = 0.54). At 48 weeks, 68.4% of subjects receiving TPV/r 500/100 mg twice daily achieved a VL less than 50 copies/mL using an intent-to-treat (ITT) analysis. The higher dosages of boosted tipranavir produced more diarrhea and intolerance compared with the unboosted doses, leading to lower viral outcomes. The durability of TPV/r was shown for up to 80 weeks (Table 1).[14]

The BI 1182.4 study randomized patients who had failed a single PI-based regimen to receive TPV/r 500/100 mg, TPV/r 1250/100 mg, or saquinavir/ritonavir 400/400 mg, each given twice daily with 2 new NRTIs.[15] Mean VL was 4.2 $\log_{10}$ in the saquinavir group and 4.46 $\log_{10}$ in both of the tipranavir arms. Using an ITT analysis, investigators determined that there were no significant differences at 16 weeks among the treatment groups (Table 1).

In BI 1182.52, 216 HIV-infected subjects, triple-class experienced (including at least 2 PI regimens, excluding fosamprenavir and atazanavir), were randomized to receive 3 different TPV/r dosing regimens plus 2 NRTIs.[16]

Table 1. Phase II Studies of Tipranavir[9,13-17]

Study/Design	Regimens	Results				
		VL[a]			Pts. with VL <50 (%)	CD4+ Change[a]
BI 1182.3 (2004)[9]		2 wk			2 wk	2 wk
OL for 2 wk	TPV/r 1200 mg bid (n = 10)	–0.77			NA	+42
N = 31 ARV naïve	TPV/r 300/200 mg bid (n = 10)	–1.43[b]			NA	+75
VL 5.02[a]	TPV/r 1200/200 mg bid (n = 11)	–1.64[b]			NA	+83
CD4+ 291[a]						
BI 1182.2 (2001),[13] (2003)[14]		24 wk	48 wk	80 wk	80 wk	80 wk
R, OL	TPV/r 500/100 mg bid (n = 19)	–2.69	–1.7	–2.55	43	+175
NNRTI naïve	TPV/r 1000/100 mg bid (n = 22)	–2.59	–2.7	–2.43	90	+143
VL 4.43[a]	plus 2 NRTIs plus EFV 600 mg qd					
CD4+ 273[a]						
BI 1182.4 (2001)[15]		16 wk			16 wk	16 wk
R, OL	TPV/r 500/100 mg bid (n = 20)	–1.44 (mean 1.30)			22	+79.8[c]
N = 62	TPV/r 1250/100 mg bid (n = 21)	–1.79 (mean 1.40)			35	–5.9[c]
VL >4[a]	SAQ/r 400/400 mg bid (n = 21)	–1.75 (mean 1.36)			30	+49.7[c]
CD4+[a,d]						
BI 1182.52 (2003)[16]		2 wk[e]		24 wk: ≥1 log ↓	24 wk	24 wk
R, DB, MC	TPV/r 500/100 mg bid (n = 72)	–0.91		31% (n = 23)	NA	+10
N = 216	TPV/r 500/200 mg bid (n = 72)	–0.96		40% (n = 29)	NA	+18
VL 4.5[a]	TPV/r 750/200 mg bid (n = 72)	–1.19		45% (n = 32)	NA	+4
CD4+ 153[a]	plus 2 NRTIs[e]					
BI 1182.51 (2004)[17,f]		2 wk		24 wk		
OL, R, parallel, MC	TPV/r 500/200 mg bid (n = 66)	1.06		1.27		
N = 315	LPV/r 400/100 mg bid (n = 79)	0.38		0.43		
VL 5.0[a]	APV/r 600/100 mg bid (n = 76)	0.15		0.47		
CD4+ 138[a,g]	SAQ/r 1000/100 mg bid (n = 75)	0.19		0.24		

APV/r = amprenavir/ritonavir; ARV = antiretroviral; DB = double-blind; CD4+ = CD4+ count in cells/mm^3; EFV = efavirenz; LPV/r = lopinavir/ritonavir; MC = multicenter; NA = not applicable; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; OL = open-label; R = randomized; SAQ/r = saquinavir/ritonavir; TPV/r = tipranavir/ritonavir; VL = HIV RNA viral load in $\log_{10}$ copies/mL.

[a]Median.

[b]$p < 0.05$ for boosted versus unboosted TPV.

[c]Mean.

[d]Median baseline CD4+ cells/mm^3: 293 for TPV/r 500/100 mg, 239 for TPV/r 1250/100 mg, and 372 for SAQ/r 400/400 mg.

[e]New NRTI added after first 2 weeks. For the first 2 weeks, the protease inhibitor was changed to TPV/r (functional monotherapy). After 2 weeks, the NRTI was changed to optimized background regimen based on genotypic testing and antiretroviral history. Approximately 75.5% of pts. started at least one new ARV after the first 2 weeks.

[f]All regimens given with an optimized background regimen.

[g]TPV/r 181 cells/mm^3, LPV/r 126 cells/mm^3, SAQ/r 115 cells/mm^3, APV/r 138 cells/mm^3.

An objective was to determine the most tolerable and effective dose to enter Phase III trials. Using ITT analysis, researchers noted no statistically significant differences in median VL endpoints among patients receiving the different TPV/r dosing regimens. However, there was a higher risk of adverse effects in those receiving the highest dosage.

Study BI 1182.51 evaluated the safety and efficacy of TPV/r and 4 single PI-containing regimens, each plus an optimized background regimen, in HIV-infected subjects who were triple-antiretroviral-class experienced and ineligible for enrollment in the RESIST (Randomized Evaluation of Strategic Intervention in Multidrug Resistant Patients with Tipranavir) trials.[17] Subjects had at least 3 mutations at codons L33F, V82A/F/L/T, I84V, or L90M and had received at least 2 PI-containing regimens with baseline VL greater than 1000 copies/mL at study entry. During the first 14 days of therapy, the median VL reduction achieved with TPV/r plus the optimized background regimen was superior to the reduction in the other arms. At 2 weeks, TPV/r was added to each of the other PI-containing arms, resulting in a transient but median VL reduction of greater than or equal to 1 $\log_{10}$ (range 0.96–1.19) in each of the PI arms at 4 weeks. Some VL reduction was maintained for 24 weeks.

In summary, Phase II studies demonstrated that TPV/r in dosages ranging from 300 to 1200 mg daily produced a 1.2–2.5 $\log_{10}$ median reduction in VL from baseline that was well tolerated and safe. Because of the more favorable safety profile observed in BI 1182.52, the TPV/r 500/200 mg dose was selected to enter Phase III trials. The BI 1182.51 study demonstrated the virologic potency of TPV/r in heavily pretreated subjects.

PHASE III

The prospective, open-label studies RESIST-1 (N = 620) and RESIST-2 (N = 863) enrolled persons with advanced HIV infection in the US/Canada/Australia or Europe/Latin America, respectively, who were triple-class-treatment experienced and had limited therapeutic options.[18-22] All subjects had received more than 2 PI-based regimens; had more than 1 primary PI mutation at D30N, M46I/L, G48V, I50V, V82A/F/L/T, I84V, or 90M and less than 2 key resistance mutations at codons L33F, V82 A/F/L/T, I84V, or L90M; and had an HIV viral load greater than 1000 copies/mL. Baseline demographics are shown in Table 2. The percentage of subjects with baseline VL greater than 100 000 copies/mL and CD4+ cell count less than 50/mm^3 was comparable for the 2 groups.[22]

Treatment response in RESIST was defined as 2 consecutive greater than or equal to l $\log_{10}$ VL reductions from baseline after randomization to receive TPV/r 500/200 mg twice daily or a comparator-boosted PI (CPI/r) plus an optimized background regimen based on genotype resistance testing and antiretroviral history. Investigators had the option of consulting an HIV resistance expert panel to assist in genotype interpretation. The specific CPI/r regimens selected are identified in Table 2.

Enfuvirtide, previously taken by 11.9% of the subjects, was provided to 27% of those receiving TPV/r compared with 22.5% in the CPI/r arm. More subjects in RESIST-1

Table 2. Demographics for RESIST-1 and RESIST-2 Studies[18-26]

Characteristic	TPV/r 500/ 200 mg bid	CPI/r[a]	p Value
Pts. (n)	746	737	
Baseline			
mean VL	4.73	4.73	
VL >100 000 (%)	37.6	39.2	
mean CD4+	196	195	
CD4+ <50 (%)	20.4	23.6	
median prior ARV, n (range)	12 (3–19)	12 (3–20)	
median prior PI (range)	4 (1–7)	4 (1–7)	
enfuvirtide experienced (%)	10.2	10.0	
Results			
enfuvirtide (%)	22.7	18.3	
VL at 24 wk (ITT, NCF)[b]			
≥1 log decline (%)	41.2	18.9[c]	<0.0001
median VL decline[d]	0.80	0.25	<0.0001
<400 (%)	34.2	14.9	<0.001
<50 (%)	23.9	9.4	<0.001
with enfuvirtide (%)	30	13	
without enfuvirtide (%)	24	9	
median CD4+ change at 24 wk[e]	34	4	<0.001
VL at 48 wk (ITT, LOCF)			
≥1 log decline (%)	33.6	15.3	<0.001
mean VL decline	1.14	0.54	< 0.0001
<400 (%)	30.4	13.8	<0.001
<50 (%)	22.8	10.2	<0.0001
mean CD4+ change at 48 wk	45	21	<0.001

APV/r = amprenavir/ritonavir; ARV = antiretroviral; CD4+ = CD4+ cell count in cells/mm^3; CPI/r = comparator-boosted protease inhibitor/ritonavir; IDV/r = indinavir/ritonavir; ITT = intent-to-treat analysis; LOCF = last observation carried forward; LPV/r = lopinavir/ritonavir; NCF = noncompleters considered failures; PI = protease inhibitor; SAQ/r = saquinavir/ritonavir; TPV/r = tipranavir/ritonavir; VL = HIV-1 RNA $\log_{10}$ copies/mL.

[a]Preselected CPI/r = LPV/r 50% (61% in RESIST-1, 38% in RESIST-2), APV/r 26% (14% in RESIST-1, 40% in RESIST-2), SAQ/r 20% (21% in RESIST-1, 20% in RESIST-2), IDV/r 4% (4% in RESIST-1, 3% in RESIST-2).

[b]24 week analysis: 81% drop-out in CPI/r arm versus 59% in TPV/r arm.

[c]LPV/r 21.4%, SAQ/r 15.3%, APV/r 18.8%, IDV/r 5%.

[d]Median VL reductions TPV/r 0.71 versus 0.28 $\log_{10}$ for LPV/r, 1.01 versus 0.20 $\log_{10}$ for SAQ/r, 1.01 versus 0.16 $\log_{10}$ for APV/r, 2.06 versus 0.40 $\log_{10}$ with addition of enfuvirtide.

[e]≥30 cells/mm^3 with TPV/r versus LPV/r (6 cells/mm^3), APV/r (0 cells/mm^3), SAQ/r (11 cells/mm^3).

(36%) received enfuvirtide than in RESIST-2 (12%).[18-22] In general, those who received enfuvirtide had more advanced HIV infection (eg, median CD4+ 72 cells/mm^3 in the TPV/r arm vs 74 cells/mm^3 in the CPI/r arm) than those not provided enfuvirtide (median CD4+ 177 and 182 cells/mm^3, respectively). An ITT analysis was employed, with missing or noncompleters considered drug failure (NCF), and last observation carried forward.

The pooled results of RESIST-1 and -2 at 24 and 48 weeks are summarized in Table 2.[18-26] At 24 weeks, the results of pooled evaluation of 1159 of the 1483 randomized RESIST patients indicated that the virologic treatment response to TPV/r was superior to response in the CPI/r arm, regardless of the degree of elevation in the baseline VL, the baseline CD4+ cell strata, the addition of enfuvirtide, or as the number of active background ARVs increased.[18-22,24-26] At 24 weeks, treatment response for subjects with baseline VL greater than 100 000 copies/mL was 34.9% in the TPV/r arm versus 13.7% in the CPI/r arm compared with 56% and 31.1%, respectively, in those with baseline VL less than 10 000 copies/mL.[22] For patients with no active background drugs, the treatment response to TPV/r was 13.1% versus 9.1% in the CPI/r arm. In patients receiving background drugs, with 1 active ARV, response was 37.4% versus 12.9%; 2 ARVs, 46.2% versus 19.9%, and 3 or more ARVs, 54.7% versus 34.3%, respectively.[27] Overall, at 24 weeks, more persons receiving TPV/r achieved a treatment response, greater reductions in VL, and immunologic benefits than did those in the CPI/r arms. These findings were maintained at 48 weeks, documenting the antiretroviral durability of TPV/r (Table 2).[20,22-24] Subjects in the TPV/r arm who received enfuvirtide also had a significantly greater CD4+ response (median increase 55 cells/mm^3; $p < 0.001$) than those in the CPI/r groups (median increase 6 cells/mm^3).

By 48 weeks, virologic failure (no treatment response) occurred in 40% of subjects receiving CPI/r compared with 10.9% of those receiving TPV/r.[23] The risk of treatment failure was significantly lower (–34%) in the TPV/r arm compared with those receiving any PI in the CPI/r arm ($p < 0.001$).[24] However, more patients receiving the CPI/r in RESIST-1 and -2 (46% and 66%, respectively) were lost to follow-up than those receiving TPV/r (15% and 43%, respectively). Using an ITT NCF analysis, the poorer response in the CPI/r arm was possibly due to the higher discontinuation rate in this group compared with the TPV/r arm.

Resistance

Although tipranavir is perceived to have a higher genetic barrier to resistance than other PIs, the resistance profile of tipranavir requires further clarification. Initially, resistance to tipranavir was thought to be associated with only 4 positional changes within the protease gene dubbed universal protease-associated mutations: L90M, V82A/L/F/S/T, I84V, and L33F/I/S/V. A cell passage study found that 10 mutations (L10F, I13V, V32I, L33F, M36I, K45I, I54V, A71V, V82L, I84V) conferred 87-fold resistance to tipranavir after 9 months.[28] Of these, 6 mutations (I13V, V32I, L33F, K45I, V82L, I84V) were found to incur a 10-fold increase in resistance.

Several studies have confirmed susceptibility to tipranavir in isolates from patients with resistance to saquinavir, nelfinavir, indinavir, and ritonavir.[5,29-31] Sensitivity to tipranavir (<4-fold IC_{50}) was maintained in 90% of isolates resistant to ritonavir, nelfinavir, and saquinavir; only 2% of these isolates were highly resistant to tipranavir (>10-fold IC_{50}).[32] Greater than 3-fold IC_{50} for TPV/r was associated with an average of 6.8 mutations, including codons V82T with I84V or I84V with L90M. Isolates from 85.4% of subjects in BI 1182.2, with baseline resistance to indinavir, nelfinavir, ritonavir, and saquinavir, maintained susceptibility to TPV/r.[33]

Reduced tipranavir susceptibility was reported with the emergence of the V82T, I84V, L90M, and L33 I/F mutations (4.6–10.1-fold change) in 6 patients treated with TPV/r for more than a year.[33] After 48 weeks, the number of mutations did not affect VL reduction; it was similar for those with either 5 or fewer or 5 or more PI mutations. This finding was also observed in the RESIST data; patients in the TPV/r arm with up to 6 primary PI mutations were able to achieve a treatment response.[18] Study BI 1182.52 found that baseline phenotypic susceptibility to TPV/r was maintained in 42% of isolates with 1-fold or less wild type (WT, median = 1.1, range 0.3–100.2); 27% greater than 1–2-fold WT, 18% with greater than 2–4-fold WT, and in 12% with greater than 4-fold WT. Susceptibility to tipranavir started to decline at an IC_{50} of approximately 2-fold WT, which required accumulation of a number of protease gene mutations.[27] A reduced median virologic response of -0.16 $\log_{10}$ was observed in patients with more than 20 mutations at baseline (16% of subjects) compared with -0.99 to -1.26 $\log_{10}$ in those with fewer mutations.[34]

In the RESIST trials, a calculated genotypic sensitivity score (GSS) indicated the total number of drugs in the optimized background regimen to which the patients' virus showed genotypic sensitivity. Data at 24 weeks found that VL responsiveness improved in the TPV/r arm versus the CPI/r arm as the number of active agents in the optimized background regimen increased. As the GSS increased from 0 to 3 or more, the percentage of subjects achieving an undetectable VL of 50 or fewer copies/mL increased from 4.9% to 34.7% in the TPV/r arm compared with from 2.6% to18.5% in the CPI/r arm. In addition, regardless of the GSS, more subjects receiving TPV/r than CPI/r achieved an undetectable viral load.[35]

A greater virologic response (ITT, NCF) was also observed with TPV/r compared with CPI/r regardless of the total number of baseline PI mutations: 12 or fewer PI mutations (50.4% vs 29.8%, respectively), 13–15 (39.4% vs 26.3%), 16 –18 (43.6% vs 13%), and 19 or more (31.7% vs 7.7%).[25] In patients with 6 primary PI mutations, more than 40% of those receiving tipranavir achieved at least a 1 $\log_{10}$ decline from baseline compared with 16.7% in the CPI/r group. Phenotypic susceptibility was maintained to tipranavir in the majority of isolates that were highly resistant to other PIs. More than a 0.5 $\log_{10}$ drop from baseline occurred during the first 8 weeks of therapy in 92% of subjects on TPV/r if the baseline IC_{50} was less than 3-fold compared with a 68% response in those with an IC_{50} 3-fold or greater.[36]

A tipranavir mutation score (number of codons with 10V, 13V, 20 M/R, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, and 84V mutations) also correlated with virologic response: 2 or fewer had a 94% response; 3–5, 84%; and 6 or more, 72% response. In ARV-experienced patients who failed TPV/r therapy after an average of 38 weeks, the most common mutations, L33V/I/F, V82T, and I 84V, along with L10V/I/S, I13V, E35D/G/N, I47V, K55R, V82L, and L89V/M, accounted for a median 14-fold decrease in tipranavir susceptibility.[4]

Adverse Effects

Severe hepatotoxicity leading to death has occurred in patients assigned to TPV in clinical trials.[4] Due to these fatalities, a black box warning has been issued. Patients with concomitant hepatitis B or C or elevated baseline transaminases have a 2.5-fold risk of developing clinical hepatitis. Close monitoring of liver function tests is warranted when initiating TPV.

The most common TPV/r adverse effects reported in clinical trials were gastrointestinal disturbances and elevations in liver transaminase, cholesterol, and triglyceride levels. In Phase II studies, nausea occurred in 31% of patients in the low- and high-dose arms; diarrhea in 26% and 72% of patients, respectively; elevated liver transaminase levels in 26% and 27% of patients, respectively; and increased triglyceride levels in 21% of patients in the low-dose arm.[9,13-15] In BI 1182.52, 15% of patients developed diarrhea and 11.6% experienced vomiting.[16]

In the RESIST-1 and -2 trials, the most common grade 2–4 adverse effects reported were diarrhea (10.9%), nausea (6.7%), pyrexia (4.6%), fatigue (4.0%), and vomiting (3.4%).[4,18-21,23] These percentages were slightly higher than those observed in the CPI/r arm (9.4%, 4.3%, 3.9%, and 3.0%, respectively). At 48 weeks, 2.1%, 24.9%, and 15.8% of patients had experienced grade 3–4 increases in cholesterol, triglyceride, and transaminase levels, respectively.[4] In both RESIST studies, these laboratory abnormalities were higher in the TPV/r arm than in the CPI/r arm (6.0%, 0.4%, and 13.0%, respectively).[21,23] Like other PIs, TPV/r has the potential to induce metabolic disturbances such as impaired glucose metabolism, hyperlipidemia, and abnormal fat redistribution syndrome.

Because tipranavir contains a sulfonamide moiety, rash may occur in patients allergic to sulfa-containing drugs.[4] Sulfonamide allergy is not an absolute contraindication, but tipranavir should be used cautiously in these patients. Rash was reported in 8–14% of patients during Phase II clinical trials and in 2% of those in the RESIST studies. When TPV/r in combination with a single dose of ethinyl estradiol was administered to healthy volunteers, 33% developed a rash. Therefore, women taking hormone replacement therapy or oral contraceptives may be at higher risk of developing a rash than are men.

An open-label safety and tolerability study of 48–144 weeks' duration (BI 1182.17) evaluated 1109 HIV-positive patients who continued TPV/r from Phase II and III clinical trials.[37] The most common adverse effects noted were similar to those reported in the compiled Phase II and RESIST studies: diarrhea (35%), nausea (24%), fatigue (13.3%), and headache (12.3%). Grade 3–4 transaminase elevations were reported in 13.4% of patients. Adverse effects were observed primarily during the first 24 weeks of therapy.

Subjects enrolled in both RESIST trials were evaluated for physical health, mental health, and quality of life, using the Medical Outcomes Study HIV Health Survey questionnaire.[38] In RESIST-1, significant improvements in mental health and a reduction of health distress were similar in patients receiving either CPI/r or TPV/r. However, in RESIST-2, significant improvements ($p < 0.05$) in pain, health distress, cognitive function, mental health, and physical health were observed in subjects receiving TPV/r compared with only role function and health distress in those receiving CPI/r. Since most questionnaire scores were higher for TPV/r than for CPI/r, TPV/r may provide improved benefits in quality of life.

Drug Interactions

The drug interaction profile for tipranavir is complex due to its coadministration with ritonavir, a strong CYP3A4 inhibitor, and further study is required. Established and potential tipranavir drug interactions and contraindications are described in Table 3. Tipranavir is both a substrate and an inducer of CYP3A4 and P-glycoprotein. Reductions in NRTI steady-state concentrations have been observed when zidovudine, stavudine, lamivudine, abacavir, and tenofovir were coadministered with TPV/r; however, the clinical significance of these findings is unknown and no dosage adjustments are currently recommended.[4,39,40] The didanosine AUC decreased from 1280 to 692 ng•h/mL in one small pharmacokinetic study of 4 HIV-infected individuals taking didanosine 200 mg twice daily with TPV/r,[39]

although a subsequent study in healthy volunteers found no changes in didanosine pharmacokinetics.[40] However, because TPV/r should be administered with food and didanosine is taken on an empty stomach, didanosine should be administered 1 hour before or 2 hours after TPV/r.

No significant changes in tipranavir or efavirenz pharmacokinetics were found during a multiple-dose study involving 24 patients.[40] Concentrations of other PIs are reduced when administered with TPV/r. Saquinavir AUC and minimum concentrations (C_{min}) are decreased by 70% and 81%, respectively; amprenavir AUC and C_{min} by 45% and 56%; and lopinavir AUC and C_{min} by 49% and 55% when coadministered with TPV/r.[17] Although the clinical significance of these interactions has not been clarified, coadministration of PIs with TPV/r is not recommended. If a dual boosted PI combination must be used, therapeutic drug monitoring may be helpful in guiding dose adjustments, particularly for combinations of TPV/r with lopinavir/ritonavir or fos-amprenavir due to substantial interpatient variability.[41,42] Laboratory models of HIV infection in peripheral blood mononuclear cells found combinations of tipranavir with lopinavir and amprenavir to be nonsynergistic.[43]

Table 3. Clinically Significant and Potential Tipranavir/Ritonavir Interactions[a]

Drugs	Comments
Drugs contraindicated for use with tipranavir/ritonavir	**Rationale**
amiodarone, astemizole, bepridil, cisapride flecainide, pimozide, propafenone, quinidine, terfenadine	potential for serious or life-threatening cardiac arrhythmias
dihydroergotamine, ergonovine, ergotamine, methylergonovine	potential for ergot toxicity
lovastatin, simvastatin	potential for serious myopathy or rhabdomyolysis
midazolam, triazolam	potential for serious or life-threatening respiratory depression or sedation
rifampin, St. John's wort	potential for decreased tipranavir concentrations, subsequent virologic failure and resistance
Drugs affected by tipranavir/ritonavir	**Recommendation**
abacavir (↓ AUC 40%)	no dose adjustment recommended; clinical significance unknown
amprenavir (↓ AUC 45%)	not recommended for concurrent use
atorvastatin (↑ AUC 900%)	start with low dose; monitor for toxicity during dosage titration
clarithromycin (↑ AUC 19%)	no dose adjustment necessary in normal renal function; reduce dose by 50% for Cl_{cr} 30–60 mL/min; reduce dose by 75% for Cl_{cr} <30 mL/min
ethinyl estradiol (↓ AUC 50%)	if used for contraception, use alternative method of hormonal contraception and/or barrier method or, if used for hormone replacement therapy, monitor for signs of efficacy
lopinavir (↓ AUC 49%)	not recommended for concurrent use
methadone (↓ AUC 50%)	consider increased dose of methadone; monitor for opioid efficacy
rifabutin (↑ AUC 290%)	reduce dose to 150 mg every other day
saquinavir (↓ AUC 70%)	not recommended for concurrent use
zidovudine (↓ AUC 35%)	no dose adjustment recommended; clinical significance unknown
etravirine (TMC-125) (AUC ↓ 76%)	do not coadminister
Drugs potentially affected by tipranavir/ritonavir	
azole antifungals	potential ↑ of itraconazole, ketoconazole, or voriconazole concentrations; use with caution; avoid fluconazole doses >200 mg/day due to risk of tipranavir toxicity
calcium-channel blockers	effects unknown; monitor efficacy and toxicity
didanosine	potential ↓ of didanosine concentrations; no dose adjustment recommended; clinical significance unknown
erectile dysfunction agents	potential ↑ of erectile dysfunction agent concentrations; do not exceed 25 mg of sildenafil in 48 h, 10 mg of tadalafil in 72 h, or 2.5 mg of vardenafil in 72 h
fluticasone	potential ↑ of fluticasone concentrations; use with caution and if benefits outweigh risks
hypoglycemic agents	effects unknown; monitor blood glucose levels
immunosuppressants	effects on cyclosporine, tacrolimus unknown; monitor immunosuppressant concentrations
metronidazole	potential antabuse-type reaction; monitor for toxicity
SSRIs, trazodone	potential ↑ of SSRI or trazodone concentrations; monitor for toxicity
TCAs	potential ↑ of TCA concentrations; consider starting at low doses with careful titration; monitor for desipramine toxicity if used concurrently
warfarin	effect unknown; monitor INR frequently
Drugs that affect tipranavir/ritonavir	
enfuvirtide ↑ TPV C_{trough} 53%	clinical significance unkown, monitor for toxicity

Cl_{cr} = creatinine clearance; INR = international normalized ratio; SSRIs = selective-serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; TPV/r = tipranavir/ritonavir.
[a]Ritonavir dose 200 mg.

In a study of 39 patients, trough concentrations of both tipranavir (+53%) and ritonavir were significantly increased in the 20 subjects receiving enfuvirtide ($p = 0.024$ and 0.012, respectively).[44] The clinical significance of this interaction is unknown and there are no current restrictions on using these antiretrovirals in combination. TMC 125 or etravirine is an investigational nonnucleoside reverse transcriptase inhibitor pending FDA approval. In a Phase III trial of 24 healthy subjects receiving the combination of TPV/r and etravirine, significant reductions in etravirine's C_{max} (-71%), C_{min} (-82%), and AUC (-76%) ($p < 0.05$ for all) were observed, prohibiting the use of this combination.[45]

Special Populations

The pharmacokinetics of TPV/r have not been studied in treatment-naïve patients, those with renal disease, pregnant women, or patients with moderate-to-severe hepatic impairment.[4] Pharmacokinetic studies in 52 children aged 2–18 years receiving TPV/r 290/115 mg/m^2 (equivalent to adult dosing) found that TPV trough concentrations, or clearance, AUC, and half-life values were similar to those observed in adults.[46] Pharmacokinetic studies are underway in pregnant women.[47] Efficacy studies are now being conducted in ARV-naïve persons and in children.[48,49]

No dosage adjustment is necessary in renal insufficiency because TPV is hepatically eliminated. However, tipranavir is contraindicated in patients with Child–Pugh B and C hepatic impairment due to concerns about potential hepatotoxicity and increased drug concentrations.[4,12] Although Phase II trials noted higher tipranavir concentrations in females than in males and more variability in concentrations in white versus black males, no dosage adjustments are warranted. Tipranavir is labeled pregnancy category C, as it has been studied in animals but not in pregnant women. Likewise, no dosage adjustments are recommended in elderly patients.[4]

Economic Considerations

The average wholesale price (AWP) of tipranavir is approximately $117.50 for a 30 day supply.[44] A limiting economic factor is the large monthly cost of $1234.45 for the required ritonavir boosting (4 capsules/day), which increases the total monthly AWP of TPV/r to approximately $2400 per month. In contrast, ARV agents that might also be considered in heavily pretreated patients with limited treatment options include lopinavir/ritonavir (AWP $703.50/mo) and, particularly, enfuvirtide (AWP $2116.93/mo). It is difficult to provide an economic comparison for TPV/r and enfuvirtide in salvage therapy because it is likely that this subset of patients will require both of these ARVs to construct an active regimen.

Therapeutic Issues

TPV/r has shown excellent antiviral activity and superiority in HIV treatment-experienced patients with resistance to multiple PIs, including lopinavir/ritonavir. It is most effective when combined with at least one other active ARV or enfuvirtide. Unfortunately, the safety and tolerability of tipranavir may not be as desirable as its efficacy. Significant gastrointestinal adverse effects occur, and a black box label warns prescribers about reports of hepatitis and hepatic failure, with some cases fatal, especially in persons coinfected with hepatitis B or C.[4]

Toxicities similar to those of other PIs, including dyslipidemia, glucose intolerance, and abnormal fat redistribution, also occur. In addition, the numerous drug interactions associated with TPV/r, many of which require further investigation, require extra vigilance for safe use of the combination agent. Both enzyme induction and inhibitory interactions with TPV/r may occur, necessitating unknown dosage adjustments. Its use with concomitant PIs is not recommended at this time. In addition, the higher boosting dosage of concomitant ritonavir may contribute to toxicity, reduced tolerability, and increased risk of drug interactions. Nevertheless, because of its activity against resistant HIV strains, TPV/r remains an important addition to existing ARV therapy regimens.

Dosage, Administration, and Patient Counseling

Tipranavir is available as 250 mg pink gelatin capsules that should be stored in the refrigerator before dispensing.[4] After the bottles are opened or the capsules dispensed, they can be stored at room temperature (15–30 °C) and used within 60 days. To be most effective, tipranavir should be administered as two 250 mg capsules plus two 100 mg capsules of ritonavir, given twice daily in conjunction with other active ARVs.

Patients should be instructed to take TPV/r with food, preferably a high-fat meal. All of the patients' concomitant medications should be reviewed with their pharmacists or physicians for identification of potential drug interactions. Antacids and didanosine should be administered 1 hour before or 2 hours after TPV/r. Due to the risk of hepatotoxicity, patients should be counseled to monitor for symptoms of hepatic dysfunction, including nausea, vomiting, fatigue, abdominal pain, light-colored stools, and yellowing of the eyes or skin, and to routinely have liver function monitored.

Formulary Recommendations/Summary

TPV/r is an essential addition to the HIV armamentarium of the formulary. It is one of only a few ARVs marketed to target the increasing problem of drug resistance. TPV/r offers significant therapeutic advantages over com-

parator PIs in the subset of HIV ARV-experienced patients harboring multiple PI mutations. Its efficacy is likely to outweigh the risks of hepatotoxicity and gastrointestinal adverse effects. Because of its expense and an unknown risk-to-benefit ratio, TPV/r is currently reserved for treatment-experienced patients failing multiple PI regimens.

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EXTRACTO

OBJETIVO: Repasar la eficacia, seguridad, farmacología, virología, farmacocinética y resistencia de tipranavir, un inhibidor de proteasa recientemente aprobado por la Administración de Drogas y Alimentos (FDA, por sus siglas en inglés).

FUENTES DE INFORMACIÓN Y SELECCIÓN DE ESTUDIOS: Se realizó una búsqueda de reportes publicados en inglés identificados a través de PubMed (1966 a febrero de 2006) utilizando los términos tipranavir ó PNU-140690. Estudios farmacocinéticos y estudios clínicos aleatorizados (publicados en forma de extracto solamente) originados en conferencias importantes sobre el VIH tales como la Conferencia de Retroviruses e Infecciones Oportunistas, la Sociedad Internacional de SIDA, la Sociedad de Enfermedades Infecciosas de América y la Conferencia Intercientífica de Agentes Antimicrobiales y Quimioterapia de los años 2000 al febrero 2006 fueron revisados para determinar la relevancia e incluídos en este repaso. Datos de la monografía del producto también fueron incluidos.

SÍNTESIS: Estudios en la fase III de investigación demuestran que tipranavir es un inhibidor de la proteasa (PI, por sus siglas en inglés) no peptídico, nuevo y efectivo para el tratamiento de VIH resistente a PIs al compararlo con otros regímenes que contienen PIs. Los efectos adversos asociados a la terapia con tipranavir/ritonavir incluyen efectos gastrointestinales, hepatotoxicidad y elevaciones en los niveles de colesterol y triglicéridos. Los datos de resistencia sugieren que el tipranavir/ritonavir debe ser reservado como terapia de rescate en pacientes que hayan fallado a tratamientos previos con terapias estándares que contengan PIs. El potencial de interacciones con

medicamentos y los costos de la terapia por la necesidad de un refuerzo con ritonavir podría limitar el uso de tipranavir.

CONCLUSIONES: La alternativa de tratamiento con tipranavir/ritonavir es esencial en el escenario de terapias antirretrovirales para pacientes de VIH que tienen opciones de tratamiento limitadas.

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RÉSUMÉ

OBJECTIF: Réviser l'efficacité, l'innocuité, la pharmacologie, la virologie, les données de pharmacocinétique et de résistance du tipranavir, un inhibiteur de la protéase récemment approuvé aux États-Unis.

REVUE DE LITTÉRATURE ET SÉLECTION DES ÉTUDES: Une recherche PubMed a été réalisée en utilisant les mots-clé tipranavir ou PNU-140690 pour la période s'étendant de 1966 à février 2006 et en se limitant aux textes de langue anglaise uniquement. Les auteurs ont également révisé et inclus dans cette revue si jugés pertinents les études de pharmacocinétique et les essais cliniques publiés seulement sous forme de résumés entre 2000 et février 2006 et émanant de congrès importants sur le VIH telles que le Conference on Retroviruses and Opportunistic Infections, l'International AIDS Society, l'Infectious Disease Society of America et l'Interscience Conference on Antimicrobials Agents and Chemotherapy.

RÉSUMÉ: Les études de phase III démontrent que le tipranavir, un nouvel inhibiteur non peptidique de la protéase, est efficace dans le traitement du VIH résistant aux inhibiteurs de la protéase (IP) lorsque comparé à d'autres régimes contenant des inhibiteurs de la protéase. Les effets indésirables associés à l'association tipranavir/ritonavir incluent des effets indésirables gastro-intestinaux, de l'hépatotoxicité et des élévations du cholestérol et des triglycérides. Les données de résistance suggèrent que l'on devrait réserver l'association tipranavir/ritonavir comme thérapie de sauvetage chez les patients déjà sous anti-rétroviraux qui ont subi un échec avec la thérapie standard incluant un IP. Son utilisation sera limitée par son potentiel d'interactions médicamenteuses et par son coût d'utilisation étant donné son association nécessaire avec le ritonavir.

CONCLUSIONS: L'association tipranavir/ritonavir est une nouvelle option thérapeutique essentielle chez les patients infectés par le VIH dont les choix de traitement sont limités.

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