**INTRODUCTION**

Highly active antiretroviral therapy (HAART) has augmented the treatment and outcome of human immunodeficiency virus (HIV-1) infection. The inclusion of protease inhibitors (PIs) with a HAART regimen has been responsible for dramatic reductions in morbidity and mortality in cases of advanced infection. It is estimated that nearly 40 million people worldwide are infected with HIV. Lack of success in achieving this target usually leads to drug-resistant variants and subsequent virological rebound.

Resistance is a principal reason for the failure of HAART. Studies are demonstrating that new infections are resulting from transmission of resistant HIV-1 strains. For HAART to work successfully, the medications must be able to recognize the virus in the blood. Sometimes, however, the virus makes copies of itself that differ from the original. This change is called a mutation. The new copies are resistant to the current regimen, and this can lead to “virological failure.” Virological failure occurs when HAART fails to reach a viral load of nondetectable status. The degree of resistance can vary; in fact, resistance usually develops gradually over time.

On June 22, 2005, the U.S. Food and Drug Administration (FDA) approved tipranavir capsules (Aptivus, Boehringer Ingelheim) for the combination antiretroviral treatment of HIV-1 infected adults. The FDA approved TPV for patients who are extremely treatment-experienced or who have HIV strains that are resistant to multiple PIs.

Tipranavir (TPV) is the first non-peptidic protease inhibitor (NPPI) developed for the treatment of HIV-1 infection. Because of its unique and potent action against virus resistance to multiple PIs, TPV serves as a relevant option in the treatment-experienced population.

**CHEMISTRY AND PHARMACOLOGY**

Protease inhibitors work at the last stage of the viral reproduction cycle. TPV is an inhibitor of the HIV-1 protease, thereby preventing cleavage of the polyprotein. This inhibition leads to the production of an immature, noninfectious virus.

The chemical structure of TPV is \( \text{N-}[3\text{-}(1\text{-R})\text{-1-}(-6\text{R})\text{-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl)}\text{-propyl[phenyl]-5-(trifluoromethyl)-2-pyridine sulfonamide}} \). Compared with the design of current PIs, the structure-based analysis design of TPV is more adaptable to alterations at the protease-binding site.

**Pharmacokinetics**

Because the lipophilic nature of TPV originally led to poor solubility, impaired bioavailability, and a large pill burden, a soft-gelatin capsule containing a self-emulsifying drug-delivery system (SEEDS) was developed to increase dissolution and bioavailability. The SEEDS formulation resulted in a two-fold increase in systemic concentrations, thereby cutting TPV’s pill burden in half.

TPV capsules, when coadministered with ritonavir (Norvir, Abbott) should also be taken with foods that are high in fat content to increase bioavailability. TPV is highly bound (at more than 99.9%) to plasma proteins, albumin, and alpha-1-acid glycoprotein.

TPV is metabolized primarily via the liver. It is both a substrate and an inducer of cytochrome CYP 3A4. When given with ritonavir, TPV becomes a potent inhibitor of CYP 3A4, and the concentration of TPV is thus increased. The addition of ritonavir increases the maximum plasma concentration \( (C_{\text{max}}) \) of TPV by 20-fold.

Elimination occurs mainly via the feces, with small amounts found in the urine. The mean elimination half-life of TPV/ritonavir in healthy volunteers and in HIV-infected adults is approximately 4.8 and 6 hours, respectively, at steady state.

**Drug Resistance**

PI-associated mutations (PRAMs) and gene mutations have led to a reduced susceptibility to the current PIs. However, resistance to TPV is associated with at least three PRAMs instead of only two PRAMs, as with the older PIs.

The flexible structure of TPV is the result of a reduced number of hydrogen bonds that are required to bind to HIV-1 protease rather than to peptide PIs. This increased flexibility reduces the likelihood of the development of PI resistance.

The effects of PI mutations on TPV resistance were analyzed in routine clinical samples. Although 90% of these isolates were resistant to multiple PIs, they showed less than a four-fold increase in the half-maximal inhibitory concentration \( (IC_{50}) \). In addition, 19 isolates demonstrated more than a 2.5-fold increase in sensitivity to TPV. Confirming data indicate that no single mutation is associated with TPV resistance.
CLINICAL TRIALS

The FDA’s approval of TPV was based on two randomized, controlled, open-label, multicenter phase 3 clinical trials, RESIST-1 and RESIST-2 (Randomized Evaluation of Strategic Intervention in Multidrug-Resistant Patients with Tipranavir). The trials enrolled a combined 1,159 triple antiretroviral class–experienced patients with a history of at least two prior PI-based antiretroviral regimens, including one therapeutic failure and at least one (but not more than two) primary protease gene mutations.

The patients received TPV in combination with ritonavir 200 mg plus an optimum background regimen (OBR) or a control regimen of an approved PI (i.e., lopinavir [Kaletra, Abbott], amprenavir [Agenerase, GlaxoSmithKline], saquinavir mesylate [Fortovase, Invirase, Roche], or indinavir sulfate [Crixivan, Merck]) in combination with ritonavir plus OBR for 24 weeks.

As observed from the trial data, TPV therapy, compared with other FDA-approved PIs, resulted in an increase in the number of virological responders. Forty percent of subjects achieved a viral load reduction of HIV-1 RNA of at least 1 log10 (the virological responders), compared with 18% for the control group. Furthermore, fewer individuals who received TPV experienced virological failure than did patients receiving approved drugs.

Thirty percent of the TPV patients were unable to achieve at least a 0.5 log10 decline from baseline and a viral RNA load below 100,000 copies by the eighth week.

Twelve percent achieved an initial response but experienced viral rebounding by week 24, whereas 7% did not respond at all, compared with 59%, 11%, and 8% for the control group, respectively. These results indicate that TPV may provide superior efficacy compared with other PIs in second-line or later regimens of antiretroviral therapy for HIV-1 infection.

The approval of tipranavir/ritonavir (TPV/r) was based on an analysis of plasma HIV-1 RNA levels in two controlled, phase 3 studies of 24 weeks’ duration. In both studies, treatment-experienced adults with evidence of HIV-1 replication, despite ongoing antiretroviral therapy, were evaluated for their responses to clinically advanced, antiretroviral agents from three drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and PIs.

In the two phase 3 studies, 40% of the HIV-1–positive patients who received TPV/r responded to treatment, whereas 18% of the comparator group responded. Treatment response was defined as a confirmed 1 log10 or greater decrease in HIV RNA copies from the baseline evaluation.

ADVERSE DRUG EVENTS

In clinical studies, adverse drug effects (ADEs) were more common in the TPV/r arm than in the standard of care comparator PI/ritonavir (CPI/r) arm in both RESIST 1 and RESIST 2 trials. Most of these ADEs were mild or moderate and asymptomatic, with the most common being gastrointestinal. Diarrhea occurred in 24.1% of patients in the TPV/r arm in the RESIST 1 trial and in 22.5% of patients in the TPV/r arm in the RESIST 2 trial.

Other ADEs that occurred in more than 10% of patients in the TPV/r arm included nausea, vomiting, fatigue, and headache.

In general, most ADEs occurred with a TPV dose of 1,200 mg. Significant laboratory abnormalities reported in RESIST 1 and RESIST 2 included elevated liver enzymes, particularly alanine transaminase (ALT), and elevated cholesterol and triglyceride levels.

Patients in both trials who had pre-existing elevated liver function test results or who had hepatitis B or C virus infection were at higher risk of experiencing elevations in AST and ALT.

In RESIST 1, elevated cholesterol and triglyceride levels were more common in the TPV/r arm than in the CPI/r arm. Elevated cholesterol levels occurred in 4.2% of patients in TPV/r arm vs. 0% of patients (P < .001) in the CPI/r arm and elevated triglyceride levels occurred in 21.7% of patients in the TPV/r arm, in contrast to 12.5% of patients (P < .01) in the CPI/r arm.

New-onset diabetes mellitus, exacerbation of pre-existing diabetes, and hyperglycemia have been reported in postmarketing surveillance data.

Mild-to-moderate skin disturbances, including urticarial and maculopapular rashes, as well as possible photosensitivity, have been reported with frequencies of 14% in females and 8% in males. In a drug-interaction trial of TPV/r and ethinyl estradiol, rashes occurred in 33% of the women participating in the study.

Other less common ADEs include bronchitis (in 2.9%), depression (in 2%), asthenia (in 1.5%), insomnia (in 1.2%), cough (in 0.8%), vertigo, mood changes, impaired concentration, and slowed thinking or movement.

Long-term studies have not been performed, but the short-term ADEs of TPV are similar to those associated with other PIs on the market. It can therefore be expected that TPV will have a long-term ADE profile similar to that of its predecessors, for example, in terms of fat redistribution.

A boxed warning on the product label for TPV states that when this drug is given with 200 mg of ritonavir, it has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection.

Boehringer Ingelheim and the FDA have informed health care professionals of important new safety information for the capsules, when administered with ritonavir (500 mg/200 mg). An addition to the drug’s boxed warning mentions reports of both fatal and nonfatal intracranial hemorrhage (ICH). The company has identified 14 reports of ICH, including eight fatalities, in 6,840 HIV–infected patients receiving TPV capsules in combination antiretroviral therapy in clinical trials. Many of the patients experiencing ICH in the TPV clinical development program had other medical conditions, such as central nervous system (CNS) lesions, head trauma, recent neurosurgery, or alcohol abuse, or they were receiving concomitant medications, including antipatelet agents, that might have caused or contributed to these events.

DRUG INTERACTIONS AND CONTRAINDICATIONS

TPV is given with ritonavir to increase its therapeutic concentration, thereby inhibiting HIV replication.

In clinical studies, TPV was an inhibitor of CYP 1A2, CYP 2C9, CYP 2C19,
and CYP 2D6, but the net effect in vivo is not known. When given with 200 mg of ritonavir, TPV is an inhibitor of CYP 3A4, and it may increase concentrations of drugs that are metabolized via this iso-enzyme. These drug interactions include:

- an increased risk of fentanyl (Duragesic, Janssen) and midazolam (Versed, Roche) toxicities accompanied by CNS and respiratory depression.
- increased serum levels of felodipine (e.g., Plendil, AstraZeneca) and potential toxicity (e.g., headache, peripheral edema, hypotension, and tachycardia).
- increased concentrations of sildenafil (Viagra, Pfizer), vardenafil (Levitra, Bayer/GlaxoSmithKline), and tadalfafil (Cialis, Eli Lilly).
- increased risk of toxicity with tacrolimus (Prograf/Astellas), including nephrotoxicity, hyperglycemia, hyperkalemia, and neuropsychiatric reactions.

The concurrent use of antiarrhythmic agents, ergot derivatives, cisapride (Propulsid, Janssen), rifampin, pimozide (Orap, Gate), midazolam, and triazolam (Halcion, Pfizer) is contraindicated because of the potential for serious or life-threatening reactions. Coadministration of TPV with lovastatin (e.g., Mevacor, Merck) and simvastatin (Zocor, Merck) is also contraindicated because of the increased risk of myopathy and rhabdomyolysis.

Because a TPV/ritonavir combination decreases the levels of abacavir sulfate (Ziagen, GlaxoSmithKline), doses of conjugated estrogens, methadone, and zidovudine (Retrovir, GlaxoSmithKline) must be adjusted according to the patient’s response. On the contrary, medications that increase plasma levels of TPV include clarithromycin (Biaxin, Abbott), fluconazol (Diflucan, Pfizer), itraconazol (Sporanox, Janssen), and ketoconazol (Nizoral, Janssen).

Drugs that decrease TPV plasma levels include antacids such as aluminum and magnesium products and magaldrate. TPV should be taken separately from antacid medications; it should be taken one hour before or two hours after antacids. When coadministered with aluminum and magnesium-based liquid antacids, TPV/ritonavir 200 mg is $2,376. This total may vary, depending on the acquisition cost for each hospital. Similar ritonavir-boosted PIs have the following AWPs:

- lopinavir/ritonavir (Kaletra, Abbott), $800
- boosted fosamprenavir calcium (Lexiva, GlaxoSmithKline/Vertex) (60 tablets), $1,200
- boosted atazanavir sulfate (Reyataz, Bristol-Myers Squibb), 200 mg (60 capsules), $1,300

CONCLUSION

HIV-1 resistance and virological failure continue to be a thorn in the side of the clinical HIV community. The large number of patients with highly resistant HIV has become a major concern as well. HIV clinicians are constantly searching for agents that will decrease the pill burden and improve medication adherence. TPV is the first nonpeptide PI developed for the treatment of HIV-1 infection. This agent is able to enter infected immune cells and inhibit HIV replication for many strains of HIV that are resistant to other commercially available PIs. The drug’s unique structure and design allow for improved potency. Because of the widespread prevalence of drug-resistant HIV, the addition of this new PI should improve the chances of achieving 100% virological suppression.

Although tipranavir offers a potent alternative for HIV-resistant patients, the boxed warning cannot be ignored. The health care community must pay close attention to the side-effect profile of TPV.

Pharmacists can expect a high level of success with HAART therapy that includes the PIs. Success is defined as achieving a therapeutic goal of less than 50 copies per milliliter of HIV RNA in plasma after four to six months of HAART. Pharmacists play a major role in reducing the risk of HIV resistance. They should encourage patients to take medications correctly as prescribed and to become knowledgeable about their medications, and they must verify that patients are picking up refills consistently to achieve total adherence.
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