PHARMACOLOGICAL AND PHARMACEUTICAL PROFILE OF DARUNAVIR: A REVIEW

Jain Ankita^{1*}, Paliwal Sarvesh¹, Pathak Shital², Kumar Manoj², Babu Lalapet Divakar²¹Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Banasthali Vidyapith, Rajasthan, India²Analytical Research Division, Ranbaxy Laboratories Limited, Gurgaon, India

Email: ankitajain135@ymail.com

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ABSTRACT

Treatment of human immunodeficiency virus (HIV) infection involves a combination of several antiviral agents belonging to different pharmacological classes. Darunavir is a second-generation protease inhibitor. It is used to treat HIV infection. Darunavir, formerly known as TMC114. Darunavir is available in the market under the trade names- Prezista®. Darunavir was designed to form robust interactions with the protease enzyme from many strains of HIV, including strains with multiple resistance mutations to second generation protease inhibitor. Darunavir is also used with small dose of ritonavir, that is darunavir is available in combination form. Combination therapy is the current standard of care for antiretroviral therapy. Since combinations of antiretroviral agents may be synergistic, additive, or antagonistic, it is important to test the developmental compounds which are used in combination with all the currently prescribed antiretroviral drugs. This combination is referred to as highly active antiretroviral therapy (HAART). This paper reviews the pharmacological and pharmaceutical properties of Darunavir. Darunavir could be an attractive target for the generic industries.

Key Words: Darunavir, Protease inhibitor, TMC114, Ritonavir

INTRODUCTION

Resistance to antiretroviral drugs have become a major challenge in designing treatment regimens for HIV-infected individuals, particularly those who have been exposed to serial monotherapy or dual-therapy before the advent of using combination antiretroviral (ARV) therapy that included non-nucleoside reverse transcriptase inhibitors (NNRTI) or protease inhibitors (PI) in the mid 1990s. In a cohort of 4306 patients having started ARV therapy with 2 nucleoside analogues, the risk of developing resistance over 6 years was 27%. The prevalence of resistance to second and third classes of ARVs in this chronically infected population was estimated to be 20% and 5%, respectively¹. Darunavir is a second-generation protease inhibitor designed to have antiviral efficacy against HIV-1. Darunavir is a second-generation protease inhibitor (PIs), designed specifically to overcome problems with the older agents in this class, such as indinavir. It is used in the treatment of HIV infection. Darunavir is available in the market under the trade names- Prezista®. Darunavir was designed to form robust interactions with the protease enzyme from many strains of HIV, including strains from treatment-experienced patients with multiple resistance mutations to second generation protease inhibitor. Darunavir, formerly known as TMC114. Prezista is an OARAC (Office of AIDS Research Advisory Council) recommended treatment option for treatment-naïve and treatment-experienced adults and adolescents².

Physicochemical Properties

Darunavir, is [(1*R*,5*S*,6*R*)-2,8-dioxabicyclo[3.3.0]oct-6-yl] *N*-[(2*S*,3*R*)-4-[(4-aminophenyl)sulfonyl-(2-methylpropyl)amino]-3-hydroxy-1-phenyl-butan-2-yl] carbamate (Figure-1) with chemical formula C₂₇H₃₇N₃O₇S and molecular weight 547.665 g/mol.

Figure 1: Structure of Darunavir

It is a peptidomimetic protease inhibitor that contains a bis-tetrahydro-furanyl (bis-THF) moiety and sulfonamide isostere; the drug is administered as its ethanolate salt [Darunavir ethanolate (Figure-2)].

Figure 2: Structure of Darunavir Ethanolate

Darunavir is structurally similar to another protease inhibitor, amprenavir. However, difference is that amprenavir has one THF ring whereas darunavir has two THF rings that are fused to each other. This bis-THF moiety reverses the stereochemistry at the bond that links it to the rest of the molecule and has a profound influence on the antiretroviral activity of darunavir³⁻⁴. Darunavir ethanolate is a white to off-white powder that is

very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol, and freely soluble in acetone and dichloromethane.

PHARMACOLOGY

Mechanism of action

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. It binds to HIV-1 protease with a K_D of 4.5×10^{-12} M.

Mechanism of action of HIV-1 protease inhibitor

Infection begins with viral entry into the host cell initiated by the interaction of viral gp120 protein with host CD4 receptor

and subsequent binding of gp120 to a co-receptor, such as chemokine receptors CCR5 (R5-tropic strains) or CXCR4 (X4-tropic strains). Interactions with the co-receptor lead to the insertion of viral gp41 protein and membrane fusion. After capsid internalization, HIV-1 reverse transcriptase catalyzes transcription of viral RNA into DNA. Transcribed viral DNA enters the nucleus of the host cell and is randomly inserted into the host genome by HIV integrase. After transcription of viral DNA into mRNA, it serves as a template for the production of viral precursor peptides. Precursor peptides are cleaved by HIV protease into active proteins and assembled, together with two copies of viral mRNA, into new viral particles at the cell surface. HIV protease inhibitors (PIs) non-competitively bind to HIV protease and inhibit its activity, leading to formation of non-infectious virions Figure-3)⁶.

Figure 3: Mechanism of action HIV-1 protease inhibitor

Antiviral Activity

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, efavirenz, or nevirapine, and the fusion inhibitor enfuvirtide⁵⁻⁶.

Pharmacokinetic and Pharmacodynamics profile

Absorption

Darunavir has an intermediate-to-high absorptive permeability in Caco-2 monolayers, indicating that darunavir would exhibit sufficient membrane permeability to obtain adequate intestinal absorption. The ratio of secretory/absorptive transport decreases with darunavir concentration, which is indicative of saturation of an active transport process (for example, P-glycoprotein [P-gp] or another efflux protein). Inhibition of transepithelial permeation of P-gp substrates by darunavir could not be excluded, but findings from a study that assessed the potential interaction between darunavir and digoxin support P-gp inhibition with darunavir in the clinic⁷.

Figure: Mean plasma concentration-time profile of Darunavir

Distribution

Darunavir is highly protein-bound. The binding of darunavir to human plasma protein (albumin and α 1-acid glycoprotein [AAG]) was determined in vitro by equilibrium dialysis of plasma samples from healthy male volunteers using 14 C-labelled darunavir. Darunavir was 95% bound to AAG and was also shown to be bound to albumin, but to a lesser extent than to AAG⁸. These findings are consistent with data obtained for almost all of the other available HIV-1 protease inhibitors⁹. The volume of distribution (V_D) was determined in a trial conducted in eight HIV-negative healthy volunteers; the mean V_D of darunavir alone was 88.1 L, while it was increased to 130 L, in the presence of ritonavir 100 mg twice daily¹⁰.

Metabolism

In vitro study of human liver microsomes indicate that darunavir primarily undergoes oxidative metabolism and is extensively metabolized by cytochrome P450 (CYP450) enzymes, mainly CYP3A. This is consistent with the metabolic pathways of other available PIs. At least three oxidative metabolites of darunavir have been identified in human liver microsomes. All these metabolites showed activity against wild-type virus, but their activity was at least 10-fold less than that of darunavir. In a darunavir mass balance study, healthy volunteers received a single dose of darunavir (400 mg) radiolabelled with the isotope 14 C and low-dose ritonavir (100 mg). After 48 hours the metabolism of 14 C darunavir was found to be extensive when darunavir was administered alone, but was markedly reduced when co-administered with ritonavir^{8,10,11}.

Elimination

The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir. After intravenous administration, the clearance of darunavir, administered alone and co-administered with 100 mg twice daily ritonavir, was 32.8 L/h and 5.9 L/h, respectively. When co-administered with ritonavir; the proportion of unchanged drug eliminated was 8% (6.8% in faeces and 1.2% in urine) and 49% (41.2% in faeces and 7.7% in

urine) in the absence and presence of ritonavir, respectively^{8,10,12}.

Therapeutic Efficacy

Additional information on special populations

Gender

Population pharmacokinetic analysis showed that HIV-infected female patients from the POWER 1 and 2 studies (n=68) had a slightly higher mean AUC_{24h} for darunavir (16.8%) compared with that observed in males. However, this difference was not considered to be clinically relevant.

Race

There was no difference in the AUC_{24h} for darunavir between people of different ethnic origins (Caucasian, Black, Hispanic, other) in a population pharmacokinetic analysis of HIV-infected patients from POWER 1 and 2.

Age

Population pharmacokinetic analysis showed that there was no marked difference in the AUC_{24h} for darunavir between the different age categories of 18–40, 40–50 and >50 years in HIV-infected patients from POWER 1 and 2, suggesting no dose modifications are required in older patients; however, there was a low number of patients aged >65 years in this analysis. In general, caution should be exercised in the administration of darunavir to elderly patients, reflecting the greater frequency of reduced hepatic function and of concomitant disease or other drug therapy. The pharmacokinetic profile of darunavir in combination with low-dose ritonavir has not been established in paediatric patients; this is currently under evaluation.

Co-infection with hepatitis B or C virus

Analysis of 24-week data from the POWER 1 study in 31 HIV-infected patients indicated that hepatitis B and/or C virus co-infection status had no apparent effect on the AUC_{24h} for darunavir.

Hepatic impairment

Darunavir is primarily metabolized and eliminated by the liver, patients with hepatic impairment might be at risk of increased plasma concentrations of darunavir.

The results of a multiple-dose study demonstrated that patients with mild or moderate hepatic impairment have an AUC for darunavir similar to that obtained for patients without hepatic impairment. Dose adjustments are not necessary in individuals with mild or moderate liver impairment, and usual clinical monitoring of these individuals receiving darunavir/ritonavir is considered adequate. This recommendation is consistent with recommendations for other protease inhibitors, as they are also metabolized by hepatic cytochrome CYP3A isoenzymes. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied.

Renal impairment

Moderate renal impairment is not expected to have a major effect on plasma concentration–time profiles for darunavir, as results from a mass balance study indicate that following darunavir administration only 7.7% of darunavir is recovered unchanged in urine. A population pharmacokinetic analysis of 20 HIV-infected patients with mild/moderate impaired renal function (creatinine clearance 30–60 ml/min) showed that the AUC for darunavir was not significantly affected. There are no pharmacokinetic data available in HIV-infected patients with severe renal impairment or end-stage renal disease. However, as the renal clearance of darunavir is limited (7.7% excreted unchanged in urine), a decrease in total body clearance is not expected in these patients. Given that darunavir and ritonavir are highly bound to plasma proteins, it is unlikely they will be removed by haemodialysis or peritoneal dialysis^{8,10,13}

Dosage and Administration

Darunavir (PREZISTA) always is given with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The prescribing information of ritonavir must therefore be consulted prior to initiation of therapy with PREZISTA/ritonavir. PREZISTA with ritonavir should be taken with food. The type of food does not affect the exposure to darunavir.

Dose: Once a daily

Darunavir (PREZISTA) should be administered 800 mg in combination with ritonavir 100 mg once a daily taken with food.

The once daily dose regimen is recommended for the following patients:

- Antiretroviral treatment-naïve patients
- Antiretroviral treatment-experienced patients with no darunavir resistance associated mutations* and who have plasma HIV-1 RNA <100,000 copies/ml.
- Antiretroviral treatment-experienced but HIV protease inhibitor-naïve patients for whom HIV-1 genotype testing is unavailable.

Dose: Twice Daily

The recommended dose of PREZISTA is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food.

The twice daily dose regimen is recommended for the following patients:

- Antiretroviral treatment-experienced patients with at least one darunavir resistance associated mutation*

- HIV protease inhibitor treatment-experienced patients for whom HIV-1 genotype testing is unavailable.
- Antiretroviral treatment-experienced patients with plasma HIV-1 RNA $\geq 100,000$ copies/ml.

* Darunavir resistance associated mutations: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, and L89V.

Dose for Paediatric patients (6 to < 18 years of age)

The recommended dose of PREZISTA/ritonavir for paediatric patients (6 to < 18 years of age and weighing at least 20 kg) is based on body weight (see table below) and should not exceed the recommended adult dose (600/100 mg Twice daily). PREZISTA tablets should be taken with ritonavir twice daily and with food. The type of food does not affect exposure to darunavir.

Table 1: Dose of combination drug (Darunavir/Ritonavir) according to body weight for Paediatric patients

Body weight (kg)	Dose
≥ 20 kg– < 30 kg	375 mg PREZISTA/50 mg ritonavir , Twice daily
≥ 30 kg–< 40 kg	450 mg PREZISTA/60 mg ritonavir, Twice daily
≥ 40 kg	600 mg PREZISTA/100 mg ritonavir, Twice daily

Contraindications

Hypersensitivity to darunavir or to any of the excipients:

Darunavir and ritonavir both are inhibitors of the CYP3A isoform. PREZISTA/ritonavir should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicinal products include astemizole, alfuzosin, sildenafil (when used for treatment of pulmonary arterial hypertension), terfenadine, midazolam, triazolam, cisapride, pimozide and the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine and methylergonovine), antiarrhythmic drugs (e.g. amiodarone, bepridil, flecainide, systemic lidocaine, quinidine).

Precautions

PREZISTA (darunavir) must be co-administered with ritonavir and food to exert its therapeutic effect. Failure to correctly administer PREZISTA with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired therapeutic effect.

Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/ritonavir. During the clinical development program (N=3063), hepatitis has been reported in 0.5% of patients receiving combination therapy with PREZISTA/ritonavir.

Haemophiliac patients

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with HIV protease inhibitors.

Diabetes Mellitus/Hyperglycaemia

New onset diabetes mellitus, hyperglycaemia, or

exacerbation of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including HIV PIs. In some of these patients the hyperglycaemia was severe and in some cases also associated with ketoacidosis.

Use in children

PREZISTA/ritonavir should not be used in children below 3 years of age in view of toxicity observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1,000 mg/kg) up to ages 23 to 26 of age.

Carcinogenicity

PREZISTA was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Systemic exposures at the highest dose (based on plasma AUC) were approximately 0.5-fold (mice) and 0.75-fold (rats) relative to humans at the recommended therapeutic dose of darunavir/ritonavir (600/100 mg, Twice daily).

Genotoxicity

PREZISTA was not mutagenic or genotoxic in a battery of in vitro and in vivo assays including bacterial reverse mutation, chromosomal aberration in human lymphocytes and in vivo micronucleus test in mice.

Use in Pregnancy

Category B2

There are no adequate and well controlled studies with darunavir in pregnant women. PREZISTA/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk. In animal studies with PREZISTA treatment up to 1000 mg/kg/day, there was no teratogenicity with darunavir in mice, rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. However, the exposure levels in mice and rats were about half those with the recommended clinical dose in humans, and only 5% in rabbits. In a pre-and post-natal rat study the pups had lower birth weight following maternal treatment with 1000 mg/kg/day darunavir.

Use in Lactation

It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse events in breast-feeding infants, mothers should be instructed not to breast-feed if they are receiving PREZISTA.

Overdosage

Effect of acute overdose of PREZISTA/Ritonavir on human is limited. Single dose up to 3200 mg of the oral solution of PREZISTA alone and up to 1600 mg of the tablet formulation of PREZISTA in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects. There is no specific antidote for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance^{5,10,14-18}.

Common Adverse Effects

Gastrointestinal Disorders:

- Abdominal pain
- Diarrhoea
- Nausea
- Vomiting

Metabolism and Nutrition Disorders:

- Anorexia

Nervous System Disorders:

- Headache

Skin and Subcutaneous Tissue Disorders:

- Pruritus
- Rash
- Urticaria

Less Common effects

Gastrointestinal Disorders

- Acute pancreatitis, dyspepsia, flatulence

General Disorders and Administration Site Conditions

- Asthenia, fatigue

Hepatobiliary Disorders

- Acute hepatitis

Immune System Disorders

- Drugs hypersensitivity
- Immune reconstitution syndrome

Metabolism and Nutrition Disorders

- Diabetes mellitus

Musculoskeletal and Connective Tissue Disorders

- Myalgia, Osteonecrosis

Psychiatric Disorders

- Abnormal dreams

Skin and Subcutaneous Tissue Disorders

- Angioedema, lipodystrophy, pruritus, Stevens Johnson Syndrome, urticaria¹⁹.

Drug Interaction

Darunavir and ritonavir both are inhibitors of CYP3A. Co-administration of darunavir and ritonavir with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse effects. Darunavir and ritonavir both are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir^{20,21}. In vitro studies have also shown varying types of interaction. Several studies have examined darunavir/ritonavir drug interactions with protease inhibitors (PIs) in healthy volunteers and HIV-infected patients; those in the former provide an insight into the possibility of interactions among HIV-infected individuals^{22,23}.

Atazanavir

The potential interaction between atazanavir/ritonavir (300/100 mg once a daily and darunavir/ritonavir (400/100 mg twice daily) has been evaluated in HIV-negative, healthy individuals. The AUC for darunavir was not affected when co-administered with atazanavir, and vice-versa. Thus, dosage adjustments of either drug in patients receiving darunavir/ritonavir and atazanavir are not considered necessary²⁴.

Indinavir

The co-administration of indinavir (800 mg twice daily) and darunavir/ritonavir (400/100 mg twice daily) was investigated in HIV-negative healthy volunteers. The mean AUC for darunavir and indinavir was increased by 24% and 23%, respectively, when these drugs were combined. These increases are deemed not to be clinically significant, and both can be co-administered without dose adjustments. Dose reductions of indinavir from 800/100 mg twice daily to 600/100 mg twice daily may be warranted, however, if the known side effect of gastrointestinal intolerance due to indinavir occurs. This result is consistent with those from studies of the combined use of indinavir and currently available ritonavir-enhanced protease inhibitor^{15,25}.

Tipranavir

No formal study on the interaction of darunavir/ritonavir and tipranavir has been conducted. However, as tipranavir markedly affects the AUC for other protease inhibitors, possibly through multiple mechanisms, it is likely to have an unfavourable interaction with darunavir/ritonavir and use of the combination is not recommended²⁶.

Drug interactions with antiretrovirals: NNRTIs

Efavirenz, nevirapine and efavirine all are non nucleoside reverse transcriptase inhibitors (NNRTIs) that are substrates for and inducers of CYP3A4 and, consequently, combined use with darunavir/ritonavir could reduce darunavir concentrations.

Efavirenz

Darunavir/ritonavir (300/100 mg twice daily) and efavirenz (600 mg once daily) were co-administered in a study involving 12 HIV-negative, healthy volunteers. The mean AUC for efavirenz was increased by 21% in the presence of darunavir/ritonavir. Conversely, the AUC for darunavir was decreased by 13% when given with efavirenz²⁷.

Nevirapine

The two-way pharmacokinetic interaction between darunavir/ritonavir (400/100 mg twice daily) and nevirapine (200 mg twice daily) was investigated in HIV-infected patients who were on stable nevirapine therapy and taking ≥ 2 NRTIs. Co-administration of nevirapine with darunavir/ritonavir caused a 24% increase in the mean AUC for darunavir compared with historical data for darunavir/ritonavir alone, and the mean AUC for nevirapine was increased by 27% when combined with darunavir/ritonavir²⁸.

Drug interactions with other drugs commonly used in HIV-infected patients:**HMG-CoA reductase inhibitors**

HMG-CoA reductase inhibitors are drugs used to lower cholesterol. A study of the interaction between darunavir/ritonavir (300/100 mg twice daily) and the HMG-CoA reductase inhibitor atorvastatin (10 mg or 40 mg once daily) in healthy volunteers indicated that low dose atorvastatin plus darunavir/ritonavir gives an atorvastatin AUC that is 15% lower than atorvastatin 40 mg once daily alone. As atorvastatin metabolism is CYP3A4-mediated, this result is expected and is presumably driven

by the ritonavir component of darunavir/ritonavir. When these drugs are combined the recommended starting dose of atorvastatin is 10 mg once daily, with a gradual dose increase tailored to response. This observation and recommendation is consistent with those from studies of other ritonavir-enhanced protease inhibitors with atorvastatin. Co-administration of pravastatin in HIV-negative, healthy volunteers as 40 mg once daily with darunavir/ritonavir (600/100 mg twice daily) caused the mean AUC for pravastatin to be increased by 81%²⁹⁻³⁰.

Drug interactions with antiretrovirals: NRTIs

There are very few clinically significant drug-drug interactions have been documented with nucleoside (tide) reverse transcriptase inhibitors (NRTIs).

However, co-administration of the NRTI tenofovir disoproxil fumarate (an ester prodrug of tenofovir) with PIs has resulted in increased concentrations of tenofovir. As tenofovir is **renally** excreted and is not a substrate, inducer or inhibitor of any CYP enzyme, the mechanism is likely to involve drug-transporter proteins³¹⁻³⁴.

Gastric pH modifiers

The pharmacokinetic interaction between darunavir/ritonavir (400/100 mg twice daily) and the gastric pH modifiers omeprazole (20 mg once daily) or ranitidine (150 mg twice daily) was investigated in HIV-negative, healthy volunteers. There was no effect on mean darunavir AUC when co-administered with either omeprazole or ranitidine, and therefore pre-emptive dose adjustment of either agent is not required. Knowledge of the interaction between PIs and gastric pH modifiers is important as, at least for atazanavir/ritonavir, co-administration with proton pump inhibitors is not recommended and with H₂ receptor antagonists, timing of administration is crucial.

Narcotic analgesics

The oral synthetic opioid methadone is given as a racemic mixture of (R)-and(S)-isomers, although only the former is the active isomer. As ritonavir is a known inducer of the metabolism of methadone, a decrease in the AUC for methadone is expected when methadone and darunavir/ritonavir are combined. The effect of darunavir/ritonavir (600/100 mg twice daily) on the pharmacokinetics of methadone was investigated in 16 HIV-negative opioid-dependent volunteers, receiving once daily methadone maintenance therapy at a stable individualized dose of 55–200 mg.

Cardiac glycosides

The two-way pharmacokinetic interaction between darunavir/ritonavir (600/100 mg twice daily) and the cardiac glycoside digoxin (0.4 mg once daily) was investigated in HIV-negative healthy volunteers. When these two drugs were combined the mean AUC for digoxin was increased by 77%, with substantial inter-individual variability. As a consequence of this interaction, it is recommended that the lowest possible dose of digoxin should initially be used, with careful titration of dose and monitoring of digoxin concentrations^{7,35-38}.

CONCLUSION

Daunavir is highly active against both wild-type and protease inhibitor (PI)-resistant HIV and appears to have a

very high genetic barrier to the development of resistance. The EC₅₀ of TMC114 against both HIV-1 and HIV-2 is in the low nanomolar range and compares favorably with EC₅₀s usually observed for the most active of the currently available protease inhibitors (PIs). Darunavir is a new protease inhibitor (PI) that represents a substantial advancement in the treatment of treatment-experienced HIV-infected patients. The pharmacokinetics of darunavir/ritonavir have been extensively studied in numerous Phase I studies as part of the clinical development programme of darunavir. In addition, the potential for interactions of darunavir/ritonavir with other drugs are well characterized and results from the studies outlined in this article can be used as guidance for the use of darunavir/ritonavir with other agents.

REFERENCES

- Kuritzkes DR. HIV resistance: frequency, testing, mechanisms. *Top HIV Med.* 2007; 15: 150–4. [PubMed]. PMID:18073450
- Ghosh AK, Dawson ZL, Mitsuya H. "Darunavir, a conceptually new HIV-1 protease inhibitor for the treatment of drug-resistant HIV". *Bioorg. Med. Chem.* 15 (24):757680. doi:10.1016/j.bmc.2007.09.010. PMC 2112938. PMID 17900913. <http://dx.doi.org/10.1016/j.bmc.2007.09.010>
- Surleraux DL, Tahri A, Verschueren WG, et al. Discovery and selection of TMC114, a next generation HIV-1 protease inhibitor. *J Med Chem* 2005;48:1813–1822.<http://dx.doi.org/10.1021/jm049560p> PMID:15771427
- Tie Y, Boross PI, Wang YF, et al. High resolution crystal structures of HIV-1 protease with a potent non-peptide inhibitor (UIC-94017) active against multi-drug-resistant clinical strains. *J Mol Biol* 2004; 338: 341–352. <http://dx.doi.org/10.1016/j.jmb.2004.02.052> PMID:15066436
- Prezista product monograph from www.janssen.com.au/files/Products/Prezista_PI.pdf. Accessed January 01, 2013.
- Warnke, D. et al. Antiretroviral drugs. *J. Clin. Pharmacol.* 2007; 47: 1570–1579.<http://dx.doi.org/10.1177/0091270007308034> PMID:18048575
- Sekar V, El Malt M, De Paepe E, et al. Effect of the HIV protease inhibitor darunavir (TMC114), coadministered with low-dose ritonavir, on the pharmacokinetics of digoxin in healthy volunteers. The Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics. Marc 21–24 2007: Anaheim, CA, USA. Abstract PII-104.
- Sekar V, Spinosa-Guzman S, Lefebvre E, Hoetelmans R. Clinical pharmacology of TMC114 – a new HIV protease inhibitor. The 16th International AIDS Conference. 13–18 August 2006, Toronto, Canada. Abstract TUPE0083.
- Schon A, Del Mar Ingaramo M, Freire E. The binding of HIV-1 protease inhibitors to human serum proteins. *Biophys Chem* 2003; 105: 221–230. [http://dx.doi.org/10.1016/S0301-4622\(03\)00071-1](http://dx.doi.org/10.1016/S0301-4622(03)00071-1)
- Tibotec Inc. PREZISTA™ (darunavir) Prescribing Information. June 2006. Available from: http://www.tibotectherapeutics.com/PREZISTA_pi.pdf. Accessed January 11, 2013.
- Winston A, Boffito M. The management of HIV-1 protease inhibitor pharmacokinetic interactions. *J Antimicrob Chemother* 2005; 56: 1–5. <http://dx.doi.org/10.1093/jac/dki184> PMID:15941777
- Sekar V, Guzman S, Stevens T, et al. Absolute bioavailability of TMC114, administered in the absence and presence of low-dose ritonavir. The 7th International Workshop on Clinical Pharmacology of HIV Therapy. 20–22 April 2006, Lisbon, Portugal. Abstract P86.
- Boffito M, Acosta E, Burger D, et al. Current status and future prospects of therapeutic drug monitoring and applied clinical pharmacology in antiretroviral therapy. *Antivir Ther* 2005; 10: 375–392. PMID:15918329
- Sekar VJ, Lefebvre E, De MT, et al. Pharmacokinetics of darunavir (TMC114) and atazanavir during coadministration in HIV-negative, healthy volunteers. *Drugs R D* 2007; 8: 241–248. <http://dx.doi.org/10.2165/00126839-200708040-00004> PMID:17596110
- Sekar V, Lefebvre E, De Marez T, et al. Pharmacokinetic interaction between the HIV protease inhibitors TMC114 and indinavir in the presence of low-dose ritonavir. The International Symposium on HIV and Emerging Infectious Diseases. June 21–23 2006, Toulon, France. Abstract PP4.15.
- Sekar V, Lefebvre E, Marien K, et al. Pharmacokinetic interaction between the HIV protease inhibitors TMC114 and saquinavir, in the presence of low-dose ritonavir. 44th Annual Meeting of the Infectious Diseases Society of America. 12–15 October 2006, Toronto, Ontario, Canada. Abstract 959.
- Katlama C. The POWER and TITAN trials: darunavir/ritonavir in the management of HIV-infected patients. *Future HIV Therapy*, 2008; 2(3): 229–245. <http://dx.doi.org/10.2217/17469600.2.3.229>
- Mills A, Nelson M, Jayaweera D et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naïve, HIV-1-infected patients: 96-week analysis. *AIDS.* 2009; 23: 1679–1688. <http://dx.doi.org/10.1097/QAD.0b013e32832d7350> PMID:19487905
- Rachlis A, Clotet B, Baxter J et al. Safety, tolerability, and efficacy of darunavir (TMC114) with low-dose ritonavir in treatment-experienced, hepatitis B or C co-infected patients in POWER 1 and 3. *HIV Clin Trials* 2007;8(4):213–20.<http://dx.doi.org/10.1310/hct0804-213> PMID:17720661
- Malaty LI, Kuper JJ. Drug interactions of HIV protease inhibitors. *Drug Saf* 1999; 20:147–169. <http://dx.doi.org/10.2165/00002018-199920020-00005> PMID:10082072
- Huang L, Wring SA, Woolley JL, et al. Induction of P-glycoprotein and cytochrome P450 3A by HIV protease inhibitors. *Drug Metab Dispos* 2001; 29: 754–760. PMID:11302944
- Molla A, Mo H, Vasavanonda S, et al. In vitro antiviral interaction of lopinavir with other protease inhibitors. *Antimicrob Agents Chemother* 2002; 46: 2249–2253. <http://dx.doi.org/10.1128/AAC.46.7.2249-2253.2002> PMID:12069982 PMID:127306
- Boffito M, Moyle GJ. Pharmacokinetic considerations for combining 2 protease inhibitors. *The AIDS Reader* 2004;14:110–116. PMID:15067999
- Sekar VJ, Lefebvre E, De MT, et al. Pharmacokinetics of darunavir (TMC114) and atazanavir during coadministration in HIV-negative, healthy volunteers. *Drugs R D* 2007; 8:241–248. <http://dx.doi.org/10.2165/00126839-200708040-00004> PMID:17596110
- Merck and Co. Inc. CRIVIVAN® (indinavir sulfate) Capsules Prescribing Information. 2006; Available from: <http://www.crixivan.com/crixivan/shared/documents/ppi.pdf>. Issued April 2006. Accessed January 21, 2013.
- Back DJ. Drug–drug interactions that matter. *Topics in HIV medicine* 2006; 14: 88–92. PMID:16835464
- Sekar V, De Pauw M, Marien K, et al. Pharmacokinetic interaction between TMC114/ritonavir and efavirenz in healthy volunteers. *Antivir Ther* 2007; 12: 509–514. PMID:17668559
- Sekar V, Lefebvre E, Marien K, et al. Pharmacokinetic interaction between the antiretroviral agents TMC114 and nevirapine, in the presence of low-dose ritonavir. 44th Annual Meeting of the Infectious Diseases Society of America. 12–15 October 2006, Toronto, Ontario, Canada. Poster 956.
- Hoetelmans R, Lasure A, Koester A, et al. The effect on TMC114, a potent next-generation HIV protease inhibitor, with low-dose ritonavir on atorvastatin pharmacokinetics. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 30–November 2, 2004, Washington DC, USA. Poster H-865.
- Sekar VJ, Spinosa-Guzman S, Marien K, et al. Pharmacokinetic drug–drug interaction between the new HIV protease inhibitor darunavir (TMC114) and the lipid-lowering agent pravastatin. 8th International Workshop on Clinical Pharmacology of HIV Therapy. 16–18 April, 2007, Budapest, Hungary. Abstract 54.
- Kruse G, Esser S, Stocker H, et al. The steady-state pharmacokinetics of nelfinavir in combination with tenofovir in HIV-infected patients. *Antivir Ther* 2005; 10: 349–355. PMID:15865230
- Piketty C, Gerard L, Chazallon C, et al. Salvage therapy with atazanavir/ritonavir combined to tenofovir in HIV- infected patients with multiple treatment failures: randomized ANRS 107 trial. *Antivir Ther.* 2006; 11: 213–221. PMID:16640102
- Kearney BP, Mathias A, Mittan A, et al. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr* 2006; 43: 278–283. <http://dx.doi.org/10.1097/01.qai.0000243103.03265.2b> PMID:17079992
- Ray AS. Role of intestinal absorption in increased tenofovir exposure when tenofovir disoproxil fumarate is co-administered with atazanavir or lopinavir/ritonavir. 7th International Workshop on Clinical Pharmacology of HIV Therapy. 20–22 April 2006, Lisbon, Portugal. Abstract 49.
- Sekar VJ, Lefebvre E, De PE, et al. Pharmacokinetic interaction between TMC114/r and omeprazole or ranitidine in HIV-negative healthy volunteers. *Antimicrob Agents Chemother* 2007; 51: 958–961. <http://dx.doi.org/10.1128/AAC.01203-06> PMID:17210768 PMID:1803132
- Sekar V, El Malt M, De Paepe E, et al. Pharmacokinetic interaction between darunavir (TMC114), a new protease inhibitor, and methadone. 8th International Congress on Drug Therapy in HIV Infection. 12–16 November 2006, Glasgow, UK. Abstract P294.
- McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. *Clin Infect Dis* 2003; 37: 476–482. <http://dx.doi.org/10.1086/376907> PMID:12905130

38. Lazzarin A, Campbell T, Clotet B, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2007; 370: 39–48. [PubMed]. [http://dx.doi.org/ 10.1016/S0140-6736\(07\)61048-4](http://dx.doi.org/10.1016/S0140-6736(07)61048-4)

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