Drugs of the Future 2007, 32(12): 1046-1052

CCC: 0377-8282/2007
DOI: 10.1358/dof.2007.032.12.1159663

Rilpivirine

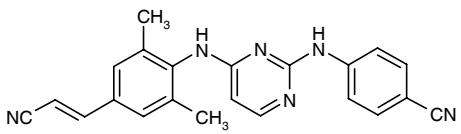
Rec INN

Reverse Transcriptase Inhibitor
Anti-HIV Agent

R-278474
TMC-278

4-[4-[4-[(*E*)-2-Cyanovinyl]-2,6-dimethylphenylamino]pyrimidin-2-ylamino]benzonitrile

InChI=1/C22H18N6/c1-15-12-18(4-3-10-23)13-16(2)21(15)27-20-9-11-25-22(28-20)26-19-7-5-17(14-24)6-8-19/h3-9,11-13H,1-2H3,(H2,25,26,27,28)/b4-3+



$C_{22}H_{18}N_6$
Mol wt: 366.4188

CAS: 500287-72-9

CAS: 700361-47-3 (monohydrochloride)

CAS: 877817-88-4 (fumarate salt [1:1])

EN: 336587

Abstract

Reverse transcriptase-mediated retrotranscription is a unique and essential characteristic of retroviruses such as the human immunodeficiency virus (HIV), and the enzyme is targeted by both nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). NNRTIs have the advantage that they bind directly to the reverse transcriptase enzyme, do not require cellular activation and are not incorporated into nascent viral DNA. Unfortunately, highly specific NNRTIs are associated with the rapid emergence of resistance mutations and extensive cross-resistance. Therefore, there is a continued need for new antiretroviral agents with increased potency, improved convenience of administration and reduced toxicity. Rilpivirine (TMC-278, R-278474) is a novel diarylpyrimidine that is easily synthesized and formulated and exhibits potent preclinical antiviral activity, high oral bioavailability and a favorable safety profile. The agent also showed antiviral efficacy as once-daily monotherapy and in combination with other antiretrovirals in clinical trials in HIV-1-infected individuals. Rilpivirine did not induce any viral genotype or phenotype changes during the study periods. Phase III clinical trials are planned to evaluate rilpivirine as a once-daily component of combination therapies for the treatment of HIV-1 infection.

Synthesis

Rilpivirine can be synthesized as follows. Chlorination of 2-(*p*-cyanophenylamino)-4-pyrimidinone (I) with refluxing $POCl_3$ gives the chloropyrimidine (II), which is condensed with ethyl 4-amino-3,5-dimethylbenzoate (III) by heating at 150 °C to afford the diamino pyrimidine (IV). Reduction of ester (IV) with $LiAlH_4$ in THF followed by re-oxidation of the obtained alcohol (V) utilizing MnO_2 in CH_2Cl_2 gives the aldehyde (VI). Then, Wittig reaction of aldehyde (VI) with cyanomethyl triphenylphosphonium chloride (VII) in the presence of *t*-BuOK provides the target cyanovinyl derivative (1, 2). In a related method, chloropyrimidine (II) is condensed with either 4-bromo- (VIIIa) or 4-iodo-2,6-dimethylaniline (VIIIb) at 150 °C to yield the corresponding diaminopyrimidines (IXa) and (IXb). Subsequent Heck coupling of aryl halides (IXa) and (IXb) with acrylonitrile (X) by means of palladium acetate and tri-*o*-tolylphosphine provides the title compound rilpivirine (1, 3). Scheme 1.

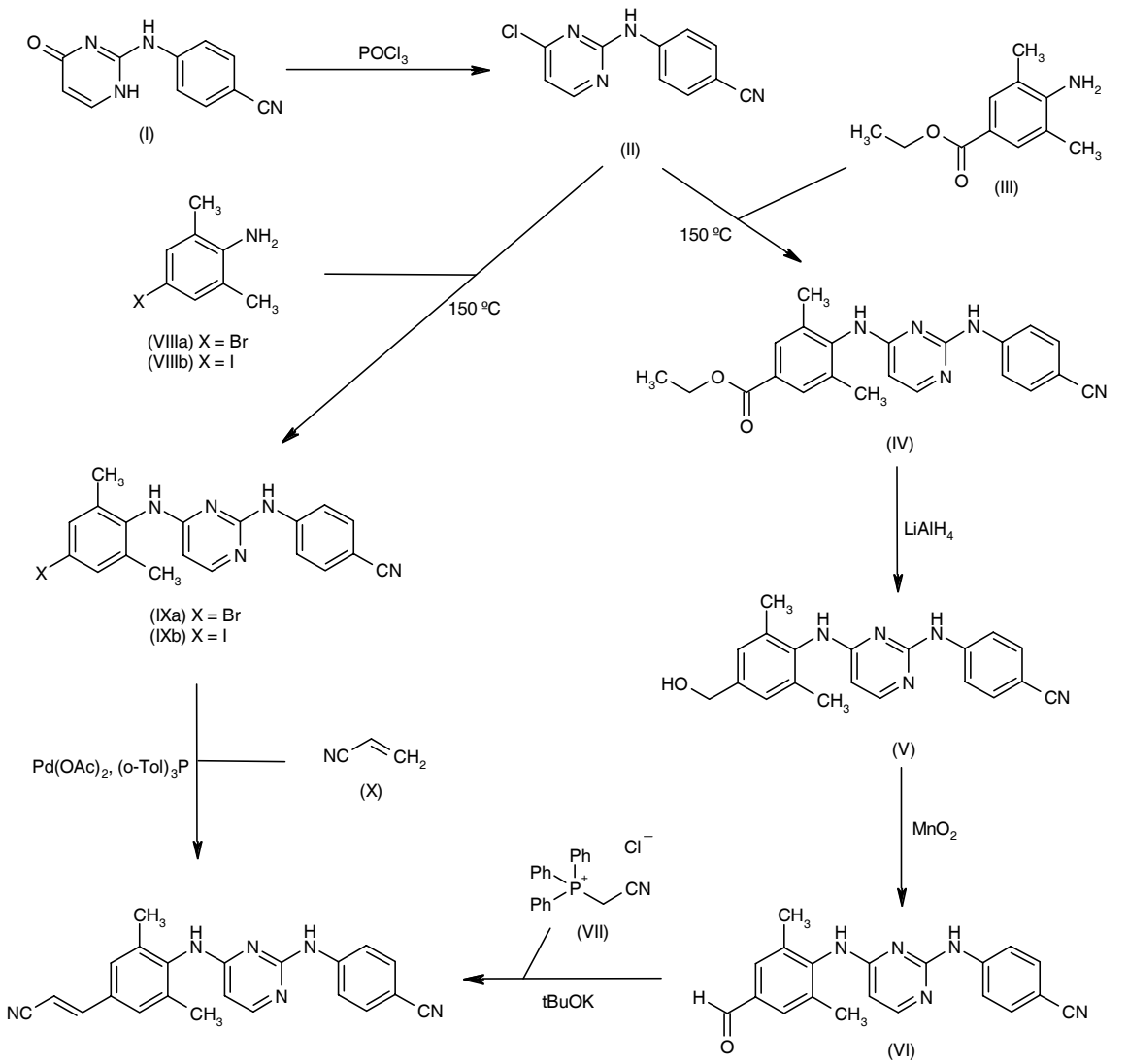
Background

The human immunodeficiency virus type 1 (HIV-1) is a retrovirus belonging to the Retroviridae family that was first identified in 1983 and was shown to be the cause of acquired immune deficiency syndrome (AIDS). According to UNAIDS (2006 report on the global AIDS epidemic [UNAIDS]), there are currently 38.6 million adults and children living with HIV/AIDS worldwide. The Centers for Disease Control (CDC) has reported that of the 850,000 to 950,000 people suspected to be infected with HIV in the U.S. alone, 180,000 to 280,000 do not know they are seropositive (4, 5).

Highly active antiretroviral therapy (HAART) incorporating at least three antiretroviral agents has been the standard therapy for HIV/AIDS for more than 10 years. HAART includes protease inhibitors (PIs), nucleoside

L.A. Sorbera, N. Serradell, E. Rosa, J. Bolós. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Rilpivirine

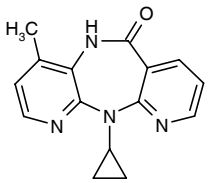


reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), entry inhibitors and integrase inhibitors. Reverse transcriptase-mediated retrotranscription is a unique characteristic of retroviruses and reverse transcriptase is a crucial enzyme for retroviral replication. The enzyme catalyzes the conversion of the single-stranded genomic RNA to double-stranded DNA with duplicated long terminal repeats, which are integrated into cellular host DNA via viral integrase. While NRTIs and NNRTIs both target reverse transcriptase, the noncompetitive NNRTIs have the advantage that they bind directly to the enzyme at the hydrophobic pocket in the p66 subunit of HIV-1 reverse transcriptase, which is close to the reverse transcriptase polymerase active site but distinct from the NRTI binding site. NNRTI binding results in distortion of the nearby reverse transcriptase polymerase site and consequent deactivation. Moreover, in contrast to NRTIs, NNRTIs do not require cellular activation and they are not incorporated into nascent viral DNA (4, 6, 7). Currently available NNRTIs for the treatment of HIV/AIDS are shown in Table I.

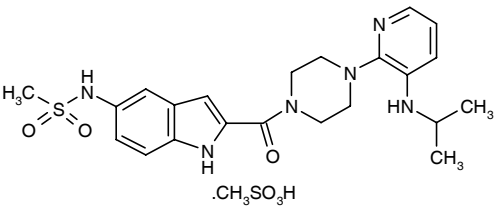
Unfortunately, the highly specific NNRTIs are associated with the rapid emergence of resistance mutations that surround the NNRTI binding pocket, thus rendering the molecules ineffective, and extensive cross-resistance is well documented among the available NNRTIs (8-11). Combination therapy has also led to the development of adherence problems, reduced antiretroviral activity and drug toxicity. As a result, there is a need for new antiretroviral agents that can enhance treatment with convenience, reduced toxicity and improved antiretroviral activity against both wild-type and drug-resistant HIV.

Table I: NNRTIs currently available or under active development for the treatment of HIV-1 infection (from Prous Science Integrity®).

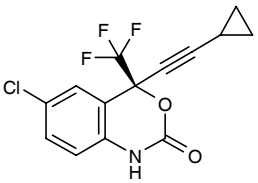
Drug	Source	Phase
1. Nevirapine	Boehringer Ingelheim	L-1996
2. Delavirdine mesilate	Pfizer	L-1997
3. Efavirenz	Bristol-Myers Squibb	L-1998
4. Etravirine	Tibotec	Prereg.
5. Rilpivirine	Tibotec	II/III
6. Amdoxovir	RFS Pharma	II
7. BILR-355 (BILR-355-BS)	Boehringer Ingelheim	II
8. UK-453061	Pfizer	II
9. UC-781*	CONRAD	I
10. Thiofoscarnet (ANX-201)	ADVENTRX Pharmaceuticals	Preclinical



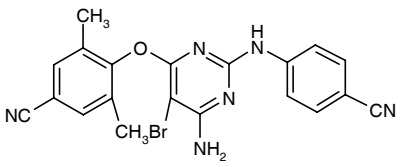
1



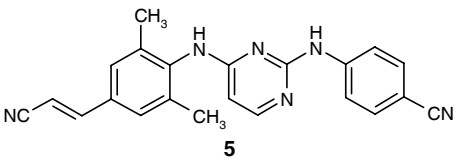
2



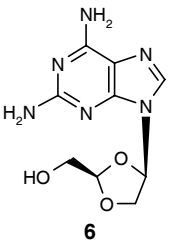
3



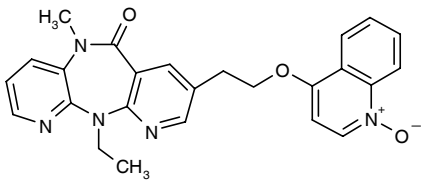
4



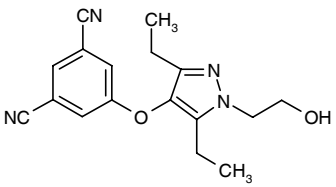
5



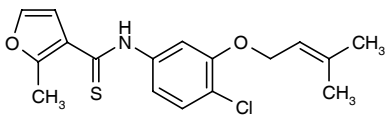
6



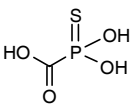
7



8



9



10

*Under development as a topical microbicide gel

Next-generation NNRTIs have been designed in an attempt to discover molecules that are easily synthesized and formulated and have high antiviral activity against wild-type and mutant viruses, high oral bioavailability and a long elimination half-life enabling once-daily administration, and minimal adverse events. Several NNRTIs under active development for the treatment of HIV/AIDS are shown in Table I.

Rilpivirine (TMC-278, R-278474) is a novel diarylpyrimidine NNRTI that was discovered after combining chemical synthesis with broad antiviral screening, bioavailability and safety evaluation. Rilpivirine showed potent antiviral activity *in vitro*, high oral bioavailability and a favorable safety profile. The agent is also easily synthesized and was selected for further development for the treatment of HIV-1 infection (1, 12, 13).

Preclinical Pharmacology

Rilpivirine displayed highly potent activity against wild-type HIV-1 (LAI, IIIB; EC_{50} = 0.5 nM) and single and double mutant HIV-1 strains in MTT assays using MT-4 cells. EC_{50} values for the single mutants 103N, 181C, 188L, 100I and 227C were 0.3, 1.26, 2, 0.4 and 2 nM, respectively, and EC_{50} values for the double mutants 103N+181C, 100I+103N (efavirenz-resistant) and 227L+106A were 1, 7.95 and 1 nM, respectively. Rilpivirine was also shown to be more potent than nevirapine, efavirenz and dapivirine against wild-type (IIIB; EC_{50} = 0.4 nM *vs.* 81, 1.4 and 1.2 nM, respectively), the single mutants L100I (EC_{50} = 0.4 nM *vs.* 597, 35 and 11 nM, respectively), K103N (EC_{50} = 0.3 nM *vs.* 2879, 28 and 2 nM, respectively), Y181C (EC_{50} = 1.3 nM *vs.* 10,000, 2 and 7 nM, respectively), Y188L (EC_{50} = 2 nM *vs.* 10,000, 78 and 37 nM; respectively) and G190S (EC_{50} = 0.1 nM *vs.* 1000, 275 and 2 nM, respectively), and the double mutant K103N+Y181C (EC_{50} = 1 nM *vs.* 10,000, 37 and 54 nM, respectively). A good selectivity index (CC_{50}/EC_{50} = 25,000-60,000) was obtained for rilpivirine (1, 12, 13).

Experiments using MT-4 cells infected with wild-type HIV-1 showed that, in contrast to efavirenz which caused viral breakthrough after 6 days of treatment, no viral breakthrough was observed after 30 days of treatment with rilpivirine. Moreover, rilpivirine did not select for resistant viruses during 30 days of exposure to 40 or 200 nM. Additional experiments using the single mutants Y181C or K103N showed that, although viral breakthrough did not occur at 40 and 200 nM rilpivirine, it was observed at 10 nM; viral breakthrough was observed for all concentrations of the agent when the K103N+Y181C mutant was used (12).

Rilpivirine was also highly active against clinical HIV isolates in a study using approximately 1,200 recombinant clinical isolates collected from HIV-infected patients. Rilpivirine at an EC_{50} of < 1 nM inhibited 81% of the isolates. In contrast, nevirapine, efavirenz and dapivirine at EC_{50} values of 10 nM or less inhibited only 18%, 69% and 79% of the isolates, respectively (12).

A crystallographic structural study examining the HIV-1 reverse transcriptase/rilpivirine complex demonstrated that rilpivirine could readily adapt to the changes in the reverse transcriptase binding pocket caused by mutations. It was suggested that this strategic flexibility of rilpivirine is responsible for the potent and broad antiviral activity of the agent, especially against drug-resistant mutations. Similar conclusions were obtained from an optical spectroscopic study examining the flexibility of rilpivirine (14-16).

Pharmacokinetics and Metabolism

Rilpivirine underwent slow glutathione-dependent conjugative metabolism in hepatocytes from humans, rats and mice *in vitro*. In contrast, the agent underwent primarily oxidative metabolism followed by sulfate conjugation or *O*-glucuronidation in dog, rabbit and monkey hepatocytes; *N*-glucuronidation was the primary route of metabolism in rabbits. The same metabolites were detected in humans, dogs, rats and mice, and only minor oxidative cytochrome P-450 (CYP)-dependent metabolites were detected. IC_{50} values for rilpivirine for inhibiting CYP3A4, CYP2C9 and CYP2D6 expressed in *Escherichia coli* were 4.6, 5 and > 10 μM, respectively (12).

More than 99% of rilpivirine was shown to bind in a concentration-dependent manner to human plasma proteins, which is typical of diarylpyrimidines. The addition of human serum albumin or human serum (50%) increased the EC_{50} value for the agent 30 times and 9-fold, respectively (12).

Pharmacokinetics were assessed in rats, dogs, rabbits and monkeys administered the compound i.v. in polyethylene glycol (PEG 400). AUC values in rats, dogs, monkeys and rabbits were 3.1 μg.h/ml following a dose of 4 mg/kg, 8.7 μg.h/ml following a dose of 1.25 mg/kg, 1.4 μg.h/ml following a dose of 1.25 mg/kg and 44 μg.h/ml following a dose of 1.25 mg/kg, respectively, with half-lives ranging from 4.4 h in rats to 31 h in dogs. Tissue:plasma ratios were 0.47-3.4 and rats showed a brain:plasma ratio of 0.5. Following oral administration in PEG 400, half-lives ranged from 2.8 h in rats to 39 h in dogs and the oral bioavailability was calculated to be about 30% in both species (12).

Results were presented from three randomized, placebo-controlled studies involving a total of 90 healthy male subjects and examining the pharmacokinetics of single (12.5-300 mg p.o.) and multiple (25-150 mg once daily p.o. for 14 days) doses of rilpivirine. Rilpivirine exhibited good absorption, with dose-proportional increases in exposure seen up to 200 mg. The mean $t_{1/2}$ values ranged from 34 to 55 h and the average C_{max} and mean $AUC_{0-\infty}$ values at 50 mg were 247 ng/ml and 7720 ng.h/ml, respectively. Because the AUC_{0-24h} value increased 2.8-fold over 14 days, it was suggested that the effective $t_{1/2}$ value was 38 h (17).

An open-label, randomized, single-dose (100 mg p.o.), crossover trial (TMC278-C102; n=12 healthy volunteers) and an open-label, randomized, multiple-dose (25, 50, 100 and 150 mg once daily p.o. for 14 days) trial (TMC278-C103; n=48 healthy volunteers) examined the effect of food on the bioavailability and pharmacokinetics of a tablet formulation of rilpivirine. In the TMC278-C102 trial, a modest increase in rilpivirine exposure was observed under fed as compared to fasted conditions; the relative bioavailability in the fed state was 145%. Dose-proportional pharmacokinetics were obtained in the TMC278-C103 study after both single and multiple doses. AUC_{24h} values on day 14 for the respective doses were 2588 ± 869, 4139 ± 1236, 9278 ± 2846 and 13,581 ± 3195 ng.h/ml. C_{max} values for the respective doses were 204 ± 76, 299 ± 98, 686 ± 202 and 1019 ± 222 ng/ml (18).

The pharmacokinetics of rilpivirine (25, 50, 100 or 150 mg once daily p.o. for 7 days) were also examined in a randomized, double-blind, placebo-controlled phase IIa trial in 47 antiretroviral-naïve HIV-infected subjects. The

pharmacokinetic parameters obtained were less than dose-proportional. Rilpivirine was rapidly absorbed on days 1 and 7. The C_{max} was reached approximately 3-4 h postdosing and plasma concentrations, which were above the target concentration of 13.5 ng/ml at all time points, increased 2-3-fold from day 1 to 7. Rilpivirine was detected in the plasma of the majority of subjects for up to 168 h following the final dose. Efficacy, tolerability and safety are discussed below (19).

Safety

Rilpivirine exhibited a promising preclinical toxicity profile. At bacteriotoxic concentrations, the agent was not mutagenic in the Ames reverse mutation test. In addition, it was negative for mutagenicity in the mouse lymphoma test and for increasing micronucleated polychromatic erythrocytes in the *in vivo* chromosomal aberration test in mice. Rilpivirine had low binding affinity for rat sodium and calcium channels and for the human ERG channel. Moreover, experiments performed using conscious telemetered dogs showed that treatment with a single dose of the agent (20, 80 and 160 mg/kg p.o.) caused no alterations in cardiovascular, pulmonary, electrophysiological or behavioral parameters (12).

In the above-mentioned phase IIa trial in 47 antiretroviral-naïve HIV-infected subjects, the agent was well tolerated. The adverse events reported were generally mild, with only 3 rilpivirine-treated subjects developing grade 2 abdominal pain, grade 2 nausea and grade 3 nausea. The most frequent adverse events were headache (14% *vs.* 18% on placebo) and gastrointestinal disorders (25% *vs.* 18.2% on placebo) (19).

Clinical Studies

The short-term antiviral efficacy of rilpivirine (25, 50, 100 or 150 mg once daily p.o. for 7 days) was evaluated in the phase IIa trial in 47 antiretroviral-naïve HIV-infected subjects. Treatment with rilpivirine resulted in a significant median reduction in plasma viral load of 1.199 $\log_{10}$ copies/ml, compared to the 0.002 $\log_{10}$ increase seen on placebo. Moreover, significantly more rilpivirine-treated subjects achieved a viral load decrease of > 1.0 $\log_{10}$ compared to placebo (25 of 36 *vs.* 0 of 11 patients). At the end of the study, 4 patients on rilpivirine achieved viral load levels below 400 copies/ml and no evidence of viral rebound was found. Gastrointestinal disorders and headache were the adverse events most commonly reported in both study groups. The antiviral activity and safety observed with rilpivirine were not significantly different among the different dose groups. No genotypic changes related to antiretroviral resistance were detected during the treatment period (19, 20).

An ongoing, randomized, active-controlled (600 mg efavirenz once daily), dose-finding study in 368 antiretroviral-naïve HIV-infected patients is comparing the efficacy, safety and tolerability of rilpivirine (25, 75 and 150 mg once daily) and efavirenz (600 mg once daily); zidovudine (AZT)/lamivudine (3TC) and tenofovir disoproxil fumarate/emtricitabine (FTC) were also used by 76% and 24% of the patients, respectively. At 48 weeks, no significant differences in antiviral activity were observed for rilpivirine and efavirenz. The percentage of patients with viral load of < 50 copies/ml ranged from 77% to 81% on all treatments, the percentage of patients with viral load of < 400 copies/ml ranged from 81% to 83% and the mean decrease in HIV-1 RNA from baseline ranged from 2.63 $\log_{10}$ copies/ml to 2.65 $\log_{10}$ copies/ml. Nausea (35.1% and 29.2%, respectively, on rilpivirine and efavirenz) and headache (18.3% and 15.7%, respectively) were the most frequent adverse events, and nervous system adverse events occurred less frequently on rilpivirine compared to efavirenz. Based on activity, safety and pharmacokinetic data, the dose of rilpivirine of 75 mg once daily was selected for further development (21).

Results have also been reported for the metabolic profiles obtained with rilpivirine and efavirenz. No significant differences in metabolic parameters were observed among the three rilpivirine dose groups. However, the mean changes in total cholesterol (+5 ± 30 mg/dl *vs.* +31 ± 30 mg/dl), high-density lipoprotein cholesterol (HDL-C; +5 ± 9 mg/dl *vs.* +12 ± 10 mg/dl), low-density lipoprotein cholesterol (LDL-C; +1 ± 25 mg/dl *vs.* +15 ± 23 mg/dl) and triglycerides (–10 ± 79 mg/dl *vs.* +18 ± 66 mg/dl) from baseline observed with rilpivirine (combined dose groups) were significantly less than the changes observed with efavirenz. Although significantly greater increases in HDL-C were seen in efavirenz-treated patients, the ratio of total cholesterol/HDL-C for the two treatment groups was not significantly different. Similar but only minimal changes from baseline were observed for glucose and insulin sensitivity for the two groups (22, 23).

Phase III trials are planned to compare the antiviral efficacy of rilpivirine and efavirenz in combination with a fixed-background regimen including tenofovir disoproxil fumarate + emtricitabine or abacavir + lamivudine in HIV-1-infected antiretroviral-naïve subjects (24, 25).

Drug Interactions

An open-label, randomized, crossover trial in 15 healthy volunteers showed that there was no pharmacokinetic interaction between rilpivirine (150 mg once daily p.o. on days 1-8 followed by a 14-day washout period) and tenofovir disoproxil fumarate (300 mg once daily on days 1-16) and therefore no dose adjustments are required when these agents are administered in combination. The agents were administered with food and both monotherapies and combination therapy were generally well tolerated. Exposure to tenofovir was significantly increased by 24% in the presence of rilpivirine, but this was considered clinically insignificant. Combination therapy resulted in an AUC_{24h} for rilpivirine and tenofovir of 102% and 124%, respectively, as compared to either agent alone. The C_{max} and C_{min} values for rilpivirine were 97% and 100%, respectively, and 121% and 124%, respectively, for tenofovir (26, 27).

Another open-label, randomized, crossover trial in 14 healthy volunteers recommended dose adjustments with co-administration of rilpivirine (150 mg once daily p.o.) and lopinavir/ritonavir (400/100 mg b.i.d.). The treatments were administered alone with food for 10 days, followed by co-administration for another 10 days. Rilpivirine alone or combined with lopinavir/ritonavir was generally well tolerated. The AUC_{24h} for rilpivirine was increased by 52% when administered in combination, possibly due to inhibition of CYP3A4 by lopinavir/ritonavir; the pharmacokinetics of the latter were not altered by co-administration (28).

Results from an open-label, randomized, single-dose, crossover trial conducted in 24 healthy volunteers administered rilpivirine alone (150 mg p.o.), 2 or 12 h after famotidine (40 mg) or 4 h before famotidine indicated that rilpivirine should be administered either 4 h before or 12 h after famotidine. The agents were administered with food and all treatments were generally well tolerated, only 3 subjects developing grade 1 or 2 adverse events; 1 subject receiving rilpivirine 12 h after famotidine discontinued due to grade 2 mouth ulcerations. The pharmacokinetics of famotidine were not altered by rilpivirine. However, the AUC_{∞} of rilpivirine was increased 13% when the agent was administered 4 h before famotidine and both the C_{max} and AUC_{∞} of rilpivirine were decreased by 85% and 76%, respectively, when rilpivirine was administered 2 h after famotidine; no alterations in these values were observed when rilpivirine was given 12 h after famotidine. A negative relationship was detected between intragastric pH and rilpivirine exposure. It was concluded that dose modifications were not warranted, although separate intake should be implemented during co-administration (29).

The findings from another open-label, randomized, crossover trial in 16 healthy subjects indicated that dose adjustments are required when rilpivirine (150 mg p.o. alone for 11 days or from day 12-22) is administered with ketoconazole (400 mg once daily for 22 days). The agents were administered with food and all treatments were generally well tolerated, with no serious adverse events observed. The C_{max}, C_{min} and AUC_{24h} of rilpivirine increased 30%, 76% and 49%, respectively, with co-administration, while the C_{max}, C_{min} and AUC_{24h} for ketoconazole decreased 15%, 66% and 24%, respectively, in the presence of rilpivirine. The increase in rilpivirine exposure observed with co-administration could be due to inhibition of CYP3A4-mediated rilpivirine metabolism by ketoconazole (30).

The pharmacokinetic interaction between rilpivirine and darunavir/ritonavir was examined in an open-label, randomized, crossover study in 16 healthy volunteers who received rilpivirine 150 mg once daily for 11 days or darunavir/ritonavir 800/100 mg once daily for 22 days with rilpivirine on days 12-22. Co-administration of darunavir/ritonavir increased exposure of rilpivirine 2-3-fold, which was suggested to be due to CYP3A4 inhibition; rilpivirine had no clinically relevant effect on darunavir exposure. Treatments were well tolerated (31).

Finally, an open-label, randomized, crossover study in 16 HIV-negative subjects evaluated the administration of atorvastatin (80 mg once daily for 5 days) or rilpivirine (150 mg once daily for 15 days) and co-administration of both drugs on days 12-15. Atorvastatin did not affect the pharmacokinetics of rilpivirine, and while exposure of the active atorvastatin metabolite 2-hydroxyatorvastatin was increased during co-administration, the exposure of unchanged atorvastatin was not affected. Dose adjustment was therefore not considered necessary for co-administration of the agents (32).

Source

Tibotec (BE, IE, US).

References

1. Guillemont, J., Pasquier, E., Palandjian, P. et al. *Synthesis of novel diarylpyrimidine analogues and their antiviral activity against human immunodeficiency virus type 1*. J Med Chem 2005, 48(6): 2072-9.

2. Guillemont, J.E.G., Palandjian, P., De Jonge, M.R. et al. (Janssen Pharmaceutica NV). *HIV inhibiting pyrimidines derivatives*. EP 1419152, JP 2005507380, US 2004198739, US 2006252764, US 7125879, WO 03016306.

3. Guillemont, J.E.G., Schils, D.P.R., Willems, J.J.M. et al. (Janssen Pharmaceutica NV). *Processes for the preparation of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile*. EP 1529032, JP 2005537303, US 2006167253, WO 2004016581.

4. Prous Science Disease Briefings: *HIV and AIDS* (online publication). Updated 2007.

5. *Centers for Disease Control and Prevention (CDC). Diagnoses of HIV/AIDS – 32 states, 2000-2003*. MMWR Morb Mortal Wkly Rep 2004, 53(47): 1106-10.

6. Kohlstaedt, L.A., Wang, J., Friedman, J.M., Rice, P.A., Steitz, T.A. *Crystal structure at 3.5 A resolution of HIV-1 reverse transcriptase complexes with an inhibitor*. Science 1992, 256(5065): 1783-90.

7. Pata, J.D., Stirtan, W.G., Goldstein, S.W., Steitz, T.A. *Structure of HIV-1 reverse transcriptase bound to an inhibitor active against mutant reverse transcriptases resistant to other nonnucleoside inhibitors*. Proc Natl Acad Sci USA 2004, 101(29): 10548-53.

8. Antinori, A., Zaccarelli, M., Cingolani, A. et al. *Cross-resistance among nonnucleoside reverse transcriptase inhibitors limits recycling efavirenz after nevirapine failure*. AIDS Res Hum Retroviruses 2002, 18(12): 835-8.

9. Van Laethem, K., Witvrouw, M., Pannecouque, C. et al. *Mutations in the non-nucleoside binding-pocket interfere with the multi-nucleoside resistance phenotype*. AIDS 2001, 15(5): 553-61.

10. Casado, J.L., Hertogs, K., Ruiz, L. et al. *Non-nucleoside reverse transcriptase inhibitor resistance among patients failing a nevirapine plus protease inhibitor-containing regimen*. AIDS 2000, 14(2): F1-7.

11. St. Clair, M.H., Martin, J.L., Tudor-Williams, G. et al. *Resistance to ddI and sensitivity to AZT induced by a mutation in HIV-1 reverse transcriptase*. Science 1991, 253(5027): 1557-9.

12. Janssen, P.A.J., Lewi, P.J., Arnold, E. et al. *In search of a novel anti-HIV drug: Multidisciplinary coordination in the discovery of 4-[[4-[[4-[(1E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile (R278474, rilpivirine)*. J Med Chem 2005, 48(6): 1901-9.

13. Van Herrewege, Y.V., Vanham, G., Michiels, J. et al. *A series of diaryltriazines and diarylpyrimidines are highly potent nonnucleoside reverse transcriptase inhibitors with possible applications as microbicides*. Antimicrob Agents Chemother 2004, 48(10): 3684-9.

14. Das, K., Bauman, J.D., Baweja, M. et al. *Strategic flexibility of the nonnucleoside RT inhibitor TMC278 explains its potency against drug-resistant mutants*. Antiviral Ther [16th Int HIV Drug Resist Workshop: Basic Princ Clin Implic (June 12-16, Bridgetown) 2007] 2007, 12(5, Suppl. 1): S33.

15. Das, K., Clark, A.D. Jr., Lewi, P.J. et al. *Roles of conformational and positional adaptability in structure-based design of TMC125-R165335 (etravirine) and related non-nucleoside reverse transcriptase inhibitors that are highly potent and effective against wild-type and drug-resistant HIV-1 variants*. J Med Chem 2004, 47(10): 2550-60.

16. Rashin, A.H.L., Steege, K.E., Lee, B.J. et al. *Spectroscopic studies of rilpirivine (TMC278/R278474) in complex with HIV-1 reverse transcriptase*. Exp Biol 2007 (April 28-May 2, Washington, D.C.) 2007, Abst 641.13.

17. de Béthune, M.-P., Andries, K., Azijn, H. et al. *TMC278, a new potent NNRTI, with an increased barrier to resistance and good pharmacokinetc profile*. 12th Conf Retroviruses Opportunistic Infect (CROI) (Feb 22-25, Boston) 2005, Abst 556.

18. Hoetelmans, R., Kestens, D., Marien, K. et al. *Effect of food and multiple dose pharmacokinetics of TMC278 as an oral tablet formulation*. 6th Int Workshop Clin Pharmacol HIV Ther (April 28-30, Quebec) 2005, Abst 80.

19. Goebel, F., Yakolev, A., Pozniak, A.L. et al. *Short-term antiviral activity of TMC278 – a novel NNRTI – in treatment-naive HIV-1-infected subjects*. AIDS 2006, 20(13): 1721-6.

20. Goebel, F., Yakovlev, A., Pozniak, A. et al. *TMC278: Potent anti-HIV activity in antiretroviral therapy-naïve patients*. 12th Conf Retroviruses Opportunistic Infect (CROI) (Feb 22-25, Boston) 2005, Abst 160.

21. Yeni, P., Goebel, F., Thompson, M. et al. *TMC278, a next-generation NNRTI, demonstrates potent and sustained efficacy in ARV-naive patients: Week 48 primary analysis of study TMC278-C204*. 11th Eur AIDS Conf (Oct 24-27, Madrid) 2007, Abst P7.2/08.

22. Ruxrungtham, K., Bellos, N., Morales-Ramirez, J. et al. *The metabolic profile of TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI)*. 4th IAS Conf HIV Pathog Treat Prev (July 22-25, Sydney) 2007, Abst TUAB105.

23. Pozniak, A., Yazdanpanah, Y., Shalit, P. et al. *TMC278, an investigational, NNRTI, has a potential benefit on lipid parameters compared with efavirenz in ARV-naive patients*. 12th Eur AIDS Conf (Oct 24-27, Madrid) 2007, Abst P9.2/05.

24. *TMC278-TiDP6-C209: A clinical trial in treatment naïve HIV-1 patients comparing TMC278 to efavirenz in combination with tenofovir + emtricitabine (NCT00540449)*. ClinicalTrials.gov Web site, November 28, 2007.

25. *TMC278-TiDP6-C215: A clinical trial in treatment naïve HIV-1 patients comparing TMC278 to efavirenz in combination with abacavir + lamivudine (NCT00543725)*. ClinicalTrials.gov Web site, November 28, 2007.

26. Hoetelmans, R., Kestens, D., Stevens, M. et al. *Pharmacokinetic interaction between the novel non-nucleoside reverse transcriptase inhibitor (NNRTI) TMC278 and tenofovir disoproxil fumarate (TDF) in healthy volunteers*. 6th Int Workshop Clin Pharmacol HIV Ther (April 28-30, Quebec) 2005, Abst 18.

27. Hoetelmans, R. et al. *Pharmacokinetic interaction between the novel non-nucleoside reverse transcriptase inhibitor (NNRTI) TMC278 and tenofovir disoproxil fumarate (TDF) in healthy volunteers*. 3rd IAS Conf HIV Pathog Treat Prev (July 24-27, Rio de Janeiro) 2005, Abst WePe3.3C15.

28. Hoetelmans, R., van Heeswijk, R., Kestens, D. et al. *Pharmacokinetic interaction between TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI) and lopinavir/ritonavir (LPV/r) in healthy volunteers*. 10th Eur AIDS Conf (Nov 17-20, Dublin) 2005, Abst PE4.3/1.

29. Van Heeswijk, R., Hoetelmans, R., Kestens, D. et al. *The pharmacokinetic (PK) interaction between famotidine and TMC278, a next generation non-nucleoside reverse transcriptase inhibitor (NNRTI), in HIV-negative volunteers*. 4th IAS Conf HIV Pathog Treat Prev (July 22-25, Sydney) 2007, Abst TUPDB01.

30. Van Heeswijk, R., Hoetelmans, R., Kestens, D. et al. *The pharmacokinetic interaction between ketoconazole and TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI), in healthy HIV-negative subjects*. 16th Int AIDS Conf (Aug 13-18, Toronto) 2006, Abst TUPE0087.

31. Van Heeswijk, R., Hoetelmans, R.M.W., Kestens, D. et al. *The pharmacokinetic (PK) interaction between TMC278, a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), and once-daily darunavir/ritonavir (DRV/r) in HIV-negative volunteers*. 47th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 17-20, Chicago) 2007, Abst H-1042.

32. Van Heeswijk, R.P.G., Hoetelmans, R.M.W., Aharchi, F. et al. *The pharmacokinetic interaction between atorvastatin and TMC278, a next generation non-nucleoside reverse transcriptase inhibitor (NNRTI), in HIV-negative volunteers*. 11th Eur AIDS Conf (Oct 24-27, Madrid) 2007, Abst P4.3/04.