Drugs of the Future 2005, 30(12): 1205-1211

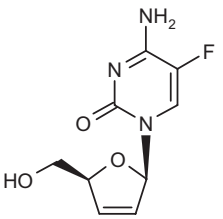
CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.12.956071

Dexelvucitabine

Anti-HIV Agent
Reverse Transcriptase Inhibitor

β-D-D4FC
DFC
DPC-817
PSI-5582
Reverse™

β-D-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine



$C_9H_{10}FN_3O_3$
Mol wt: 227,1925

CAS: 181785-83-1

EN: 260501

Abstract

The nucleoside reverse transcriptase inhibitors (NRTIs) are widely used in combination with protease inhibitors and non-nucleoside RT inhibitors (NNRTIs) in regimens of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) infection. However, these regimens may lack efficacy, or initially successful regimens may fail because of significant cross-resistance among agents of the same class. The development of second-generation NRTIs has focused on the resistance profile and the requirement for suppression of mutant variants likely to be present in NRTI-experienced patients. Dexelvucitabine (Reverset™) is a cytidine nucleoside analogue that combines potency against wild-type, zidovudine- and lamivudine-resistant variants of HIV reverse transcriptase. It is a potent inhibitor of HIV-1 replication *in vitro*, with activity against recombinant zidovudine- and lamivudine-resistant viruses. A phase IIb study conducted in 199 treatment-experienced patients who were viremic on their current regimen showed a decrease in mean viral load of 1.2 $\log_{10}$ copies/ml and indicated that dexelvucitabine provided sustained antiviral activity in patients with multiple resistance mutations, including M184V and K65R.

Synthesis

Dexelvucitaine can be prepared by several ways:

1) Acylation of 2,3-*O*-isopropylidene-α-D-xylofuranose (I) with benzoyl chloride and pyridine gives the dibenzoyl ester (II), which is deprotected by means of H_2SO_4/AcOH in hot THF to yield 3,5-di-*O*-benzoyl-α-D-xylofuranose (III). Reaction of (III) with PPh_3, I_2 and imidazole in dichloromethane followed by the glycosylation of the *N*,*O*-disilylated-5-fluorocytosine (V) with *N*-iodosuccinimide (NIS) in CH_2Cl_2, provides the 2'-α-iodonucleoside (VI). Treatment of (VI) with Zn in EtOH/ethyl acetate, using AcOH as catalyst, gives the unsaturated nucleoside (VII), which is finally debenzoylated with butylamine in THF (1). Scheme 1.

2) Protection of lactone (VIII) with TBDPS-Cl and imidazole in DMF affords intermediate (IX), which by reaction first with TMS-Cl by means of LiHMDS in THF, and then with phenylselenenyl bromide yields the selenoderivative (XI). Reduction of (XI) with DIBALH in toluene followed by acetylation with Ac_2O provides the β-D-*erythro*-pentofuranose (XII) (2). Condensation of (XII) with the protected fluorocytosine (V), using either TMS-OTf or $SnCl_4$, gives the selenium-containing nucleoside (XIII), which is then submitted to an oxidative elimination with H_2O_2 and pyridine in CH_2Cl_2 to yield the unsaturated nucleoside (XIV). Finally (XIV) is desilylated withTBAF in THF (3). Similar synthetic pathway has been described using thiafuranose intermediates instead of selenofuranose derivatives (4). Scheme 2.

3) Bromoacetylation of 5-fluorocytidine (XV) with 2-acetoxyisobutyryl bromide (XVI) in acetonitrile/ethyl acetate gives a mixture of two main bromoacylated compounds (XVII and XVIII). Reductive elimination of this mixture with Zn/Cu in MeOH/AcOEt or DMF yields the unsaturated cytidine derivative (XIX), which is finally deprotected by means of NaOMe in methanol (5).

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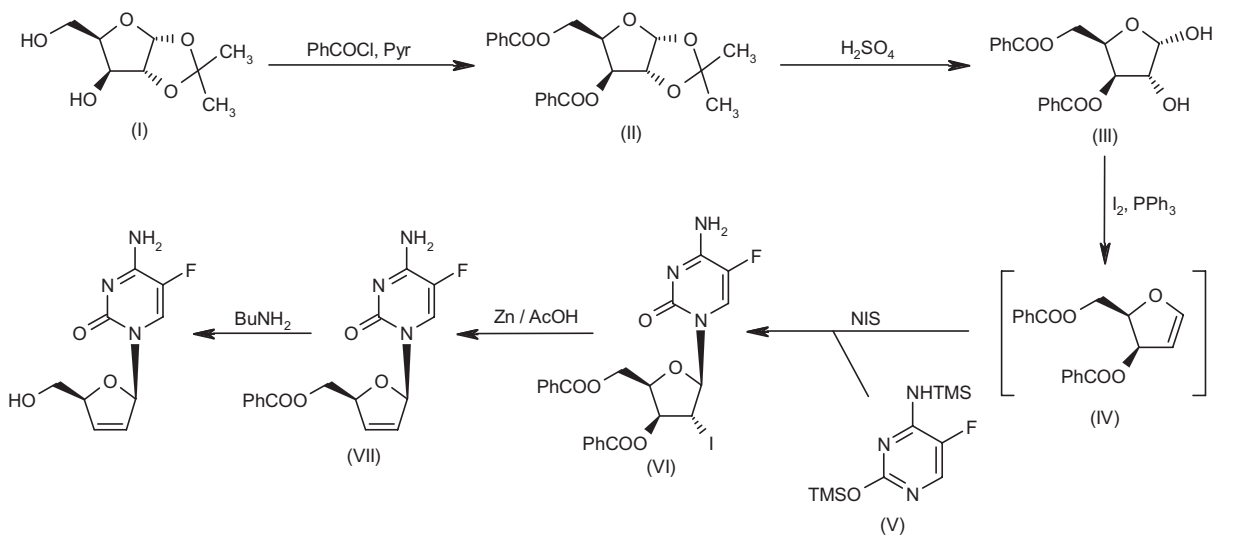
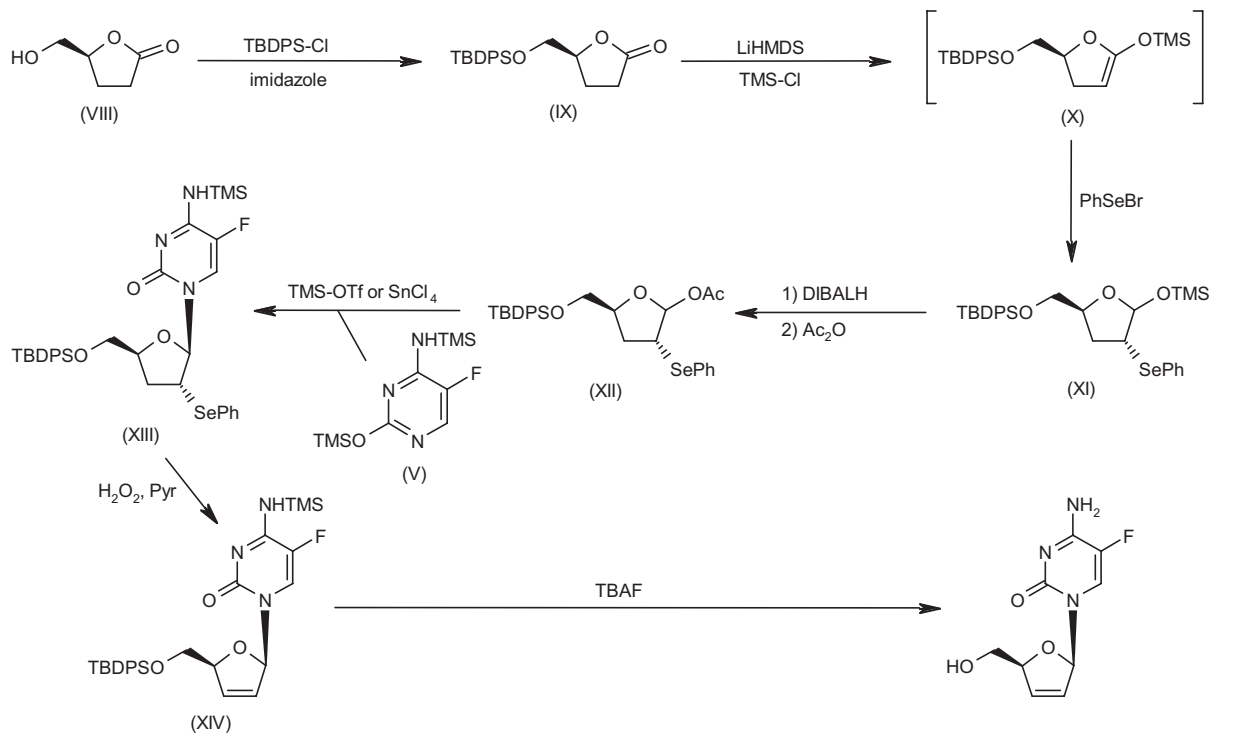
Scheme 1: Synthesis of Dexelvucitabine



Scheme 2: Synthesis of Dexelvucitabine



A similar process using Zn in the reductive elimination step and a novel procedure for the removal of the divalent zinc has been disclosed recently (6). Scheme 3.

4) Bromoacetylation of 5-fluorouridine (XX) with 2-acetoxyisobutyryl bromide (XVI) in acetonitrile gives gives a mixture of two main bromoacylated uridines (XXI) and (XXII). This mixture is treated with Zn/AcOH in DMF to yield the unsaturated uridine derivative (XXIII). Reaction of (XXIII) with 1,2,4-triazole (XXIV) by means of $POCl_3$ and TEA in acetonitrile affords the triazolyl intermediate (XXV), which is treated with ammonia in MeOH to provide the cytidine derivative (XIX) and finally deacylated with NaOMe in methanol (5). Scheme 4.

5) Reaction of thymidine (XXVI) with PPh_3 and DIAD in THF gives anhydrothymidine (XXVII), which is treated with NaOH in THF/water to yield 3'-β-OH-derivative (XXVIII). Protection of (XXVIII) with TBDPS-Cl in pyridine affords the 5'-*O*-silylated intermediate (XXIX), which after reaction with ammonium sulfate in refluxing HMDS provides the silylated glycal (XXX). Partial deprotection of (XXX) with K_2CO_3 in THF/MeOH gives intermediate (XXXI), which is condensed with phenyl isocyanate (XXXII) by means of DBU in CH_2Cl_2 to yield the carbamate (XXXIII). *In situ* activation of (XXXIII) with a Pd complex in CH_2Cl_2 followed by reaction with the appropriate protected 5-fluorocytosine by means of DBU in THF/DMF affords the protected nucleoside (XXXIV), which is finally deprotected by standard methods (7). Scheme 5.

Introduction

The successful treatment of human immunodeficiency virus (HIV) infection relies upon combination regimens of antiretroviral drugs. The nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of antiretroviral drugs available for the treatment of HIV infection. The discovery of potent inhibitors of the viral protease led to the development of combination regimens of NRTIs, protease inhibitors and non-nucleoside RT inhibitors (NNRTIs), known as highly active antiretroviral therapy (HAART) regimens. These regimens have demonstrated efficacy against HIV disease, improving virological, immunological and clinical endpoints, and their prolonged use has resulted in a substantial reduction in morbidity and mortality associated with HIV infection. There are currently four classes of drugs (NRTIs, NNRTIs, protease inhibitors and entry inhibitors) used for the treatment of HIV-infected individuals and within these classes there are over 20 individual antiretroviral drugs approved by the U.S. FDA. However, despite the many possibilities for drug combinations, the effectiveness of regimens is reduced because of significant cross-resistance among agents of the same class. Other reasons for poor antiviral responses or failure of initially successful regimens include complexity of the regimen, frequency of dosing, variable plasma concentrations and drug toxicity. The successful treatment of antiretroviral-experienced patients is the greatest challenge in the clinical management of HIV-infected individuals (8, 9).

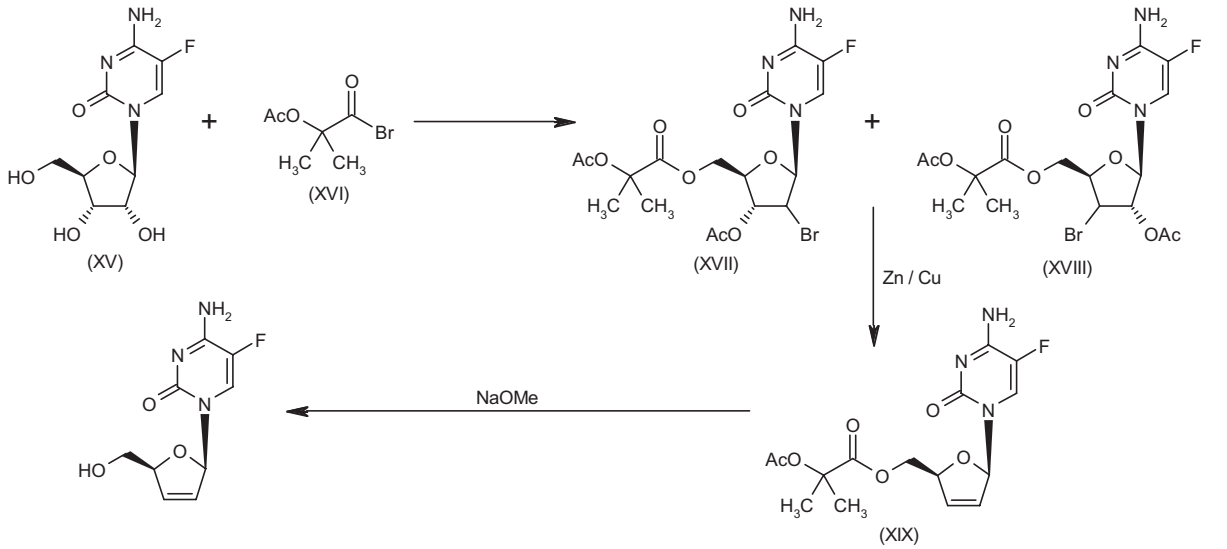
The NRTIs are structural analogues of endogenous nucleic acids. A series of phosphorylation reactions results in their conversion to the active triphosphate form, which acts as an alternative substrate for HIV reverse transcriptase, resulting in premature chain termination and impaired transcription. Certain key mutations are involved in cross-resistance to this class of drugs. The development of second-generation NRTIs has focused on the resistance profile and the requirement for suppression of mutant variants likely to be present in NRTI-experienced patients (3, 8). Dexelvucitabine (D-d4FC, PSI-5582, DPC-817, Reverset™ is a cytidine nucleoside analogue that combines potency against wild-type, zidovudine- and lamivudine-resistant variants.

Pharmacological Actions

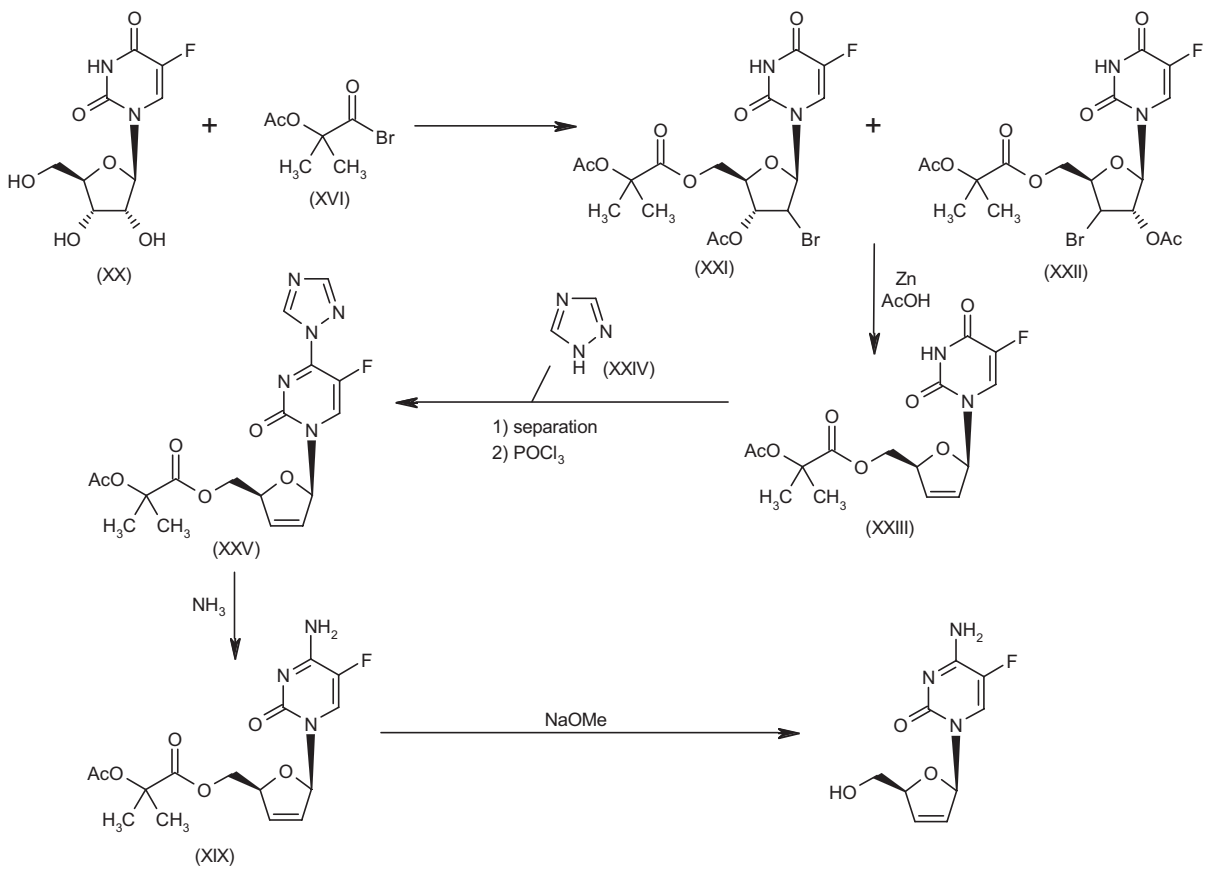
Dexelvucitabine is a potent inhibitor of HIV-1 replication *in vitro*, with IC_{90} values ranging from 0.4 μM to 1.5 μM against a panel of laboratory strains and clinical isolates in various cell lines (MT-2, peripheral blood mononuclear cells [PBMCs]), and low cytotoxicity in normal cells (IC_{50} > 30 μM) (1, 3, 10-12). Dexelvucitabine is rapidly converted to the active triphosphate, which potently inhibits HIV-1 reverse transcriptase (IC_{50} = 0.14-0.27 μM against recombinant enzyme) (3, 10, 12-14), showing some selectivity relative to cellular polymerases (IC_{50} = 0.74-1.20 μM for inhibition of cellular repair enzyme DNA polymerase β and mitochondrial DNA polymerase γ) (10). Dexelvucitabine also showed potent antiviral activity against recombinant mutant variants of HIV-1, including those with multiple substitutions in reverse transcriptase associated with resistance to zidovudine and lamivudine, such as M184V, M41L, D67N, K70R, T215Y and K219Q (IC_{50} = 0.08-1.28 μM; IC_{90} = 0.6-10.2 μM). The highest degree of resistance was observed in viruses containing the K65R point mutation (9.3-fold resistance relative to wild-type virus) (10-12). Dexelvucitabine was also reported in early studies to be active against hepatitis B virus (HBV) (13, 14).

A panel of 50 viruses carrying reverse transcriptases derived from HIV clinical isolates displaying a wide range of NRTI resistance mutations were examined in order to describe a detailed resistance profile for dexelvucitabine. The median fold increase in effective viral concentration for the panel of viruses was 3.2, which was comparable to tenofovir and didanosine. Dexelvucitabine retained full activity against recombinant zidovudine- and lamivudine-resistant viruses, but was less potent against multi-NRTI-resistant viruses, especially those carrying the Q151M cluster of mutations. Serial passage experiments in MT-4 cells revealed the emergence of virus containing the K65R mutation, which conferred 5.3-8.7-fold resistance to dexelvucitabine (15). Further studies demonstrated that resistance to dexelvucitabine emerged only after prolonged exposure in MT-2 cells, but resistance could not be selected in PBMCs. In addition to K65R and V179D mutations, three novel mutations (K70N, V90I and R172K) were identified. In general, the mutants exhibited low-level resistance to the drug (16-18).

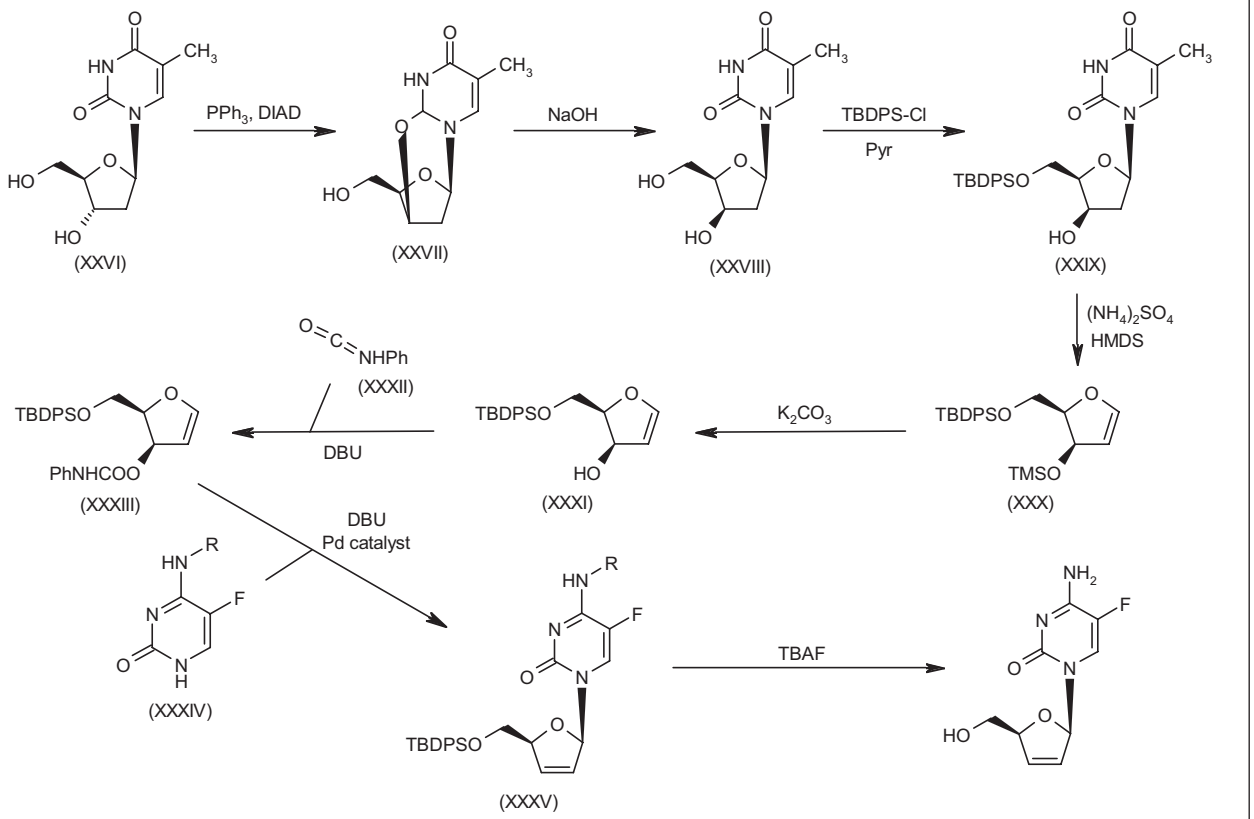
Scheme 3: Synthesis of Dexelvucitabine



Scheme 4: Synthesis of Dexelvucitabine



Scheme 5: Synthesis of Dexelvucitabine



In vivo, dexelvucitabine was shown to reduce virus levels in peritoneal cells, lymph node, spleen and blood in huPBMC SCID mice treated with a dose of 60 mg/kg/day i.p. b.i.d. (12, 19).

Pharmacokinetics and Metabolism

In human PBMCs, the uptake and conversion of dexelvucitabine to the active triphosphate were rapid. The metabolite had an intracellular half-life of 13-17 h. The concentrations of intracellular triphosphate exceeded those required for 50% inhibition of wild-type HIV-1 reverse transcriptase and the K_i for the M184V mutant reverse transcriptase. The long intracellular half-life of the active metabolite indicated that once- or twice-daily dosing may be sufficient to maintain levels in excess of those required for inhibition of the reverse transcriptase from both wild-type HIV-1 and mutant variants likely to be present in individuals exposed to zidovudine and/or lamivudine (10, 20).

The effect of other nucleosides on the formation of the triphosphate was evaluated in PBMCs. Cells were exposed to 5 μM dexelvucitabine plus variable concentrations of nucleoside analogues for 24 h. The adenosine analogue didanosine, the thymidine analogue stavudine and the guanosine analogue abacavir had no effect on the level of triphosphate observed. At the highest concentration (7 μM), zidovudine caused a 19% decrease and lamivudine a 14% decrease in the observed level of triphosphate. *In vitro* combination studies using the method of biological ratios identified combinations of dexelvucitabine with NNRTIs and protease inhibitors that were additive to synergistic at the enzyme level. When combined with other cytidine analogues, no antagonism was observed, indicating that the enzymes involved in the cytidine kinase pathway may not be rate-limiting for the production of the triphosphate (20).

Pharmacokinetic parameters of dexelvucitabine were determined using a 2-compartment model after the administration of a single dose to rhesus monkeys. Monkeys were administered 33.3 mg/kg orally and intravenously with a 3-week washout period between doses. The mean maximum concentration of the drug in serum (C_{max}) and the time to C_{max} (t_{max}) were 33.4 μM and 2.67 h, respectively, following oral administration. The mean terminal elimination half-life was 3.6 h (i.v.). The mean oral bioavailability of dexelvucitabine was 41%, and the principal route of elimination was via the kidney. Levels of dexelvucitabine in plasma and cerebrospinal fluid were higher than the median effective concentration (EC_{50}) for

HIV-1 *in vitro* following both routes of administration (12, 14, 21).

Clinical Studies

The pharmacokinetics and safety of single oral doses of dexelvucitabine were evaluated in a randomized, double-blind, placebo-controlled, crossover phase I study in 18 HIV-infected male subjects who had not previously received antiretroviral therapy. Five dose levels (10, 25, 50, 100 and 200 mg) of dexelvucitabine were evaluated in 3 cohorts of subjects. Doses of 10, 25 and 50 mg were administered as a buffered solution and higher doses (50-200 mg) were administered as enteric-coated tablets. Dexelvucitabine showed high oral bioavailability and was well tolerated at all dose levels. C_{max} and area under the curve (AUC) values increased linearly with dose. A C_{max} of 4.95 μM, consistent with the concentration necessary to suppress viral replication in vitro, was achieved at the 100-mg dose. Quantification of viral RNA demonstrated that a single oral dose of dexelvucitabine significantly reduced plasma viral load by 0.45 ± 0.10 $\log_{10}$ copies/ml at 48 h. At the lowest dose, a mean decrease of 0.37 ± 0.10 $\log_{10}$ copies/ml was obtained (22-24).

A 10-day double-blind, placebo-controlled monotherapy study was performed in 30 HIV-infected treatment-naïve individuals with $CD4^+$ cell counts > 50 cells/mm^3 and HIV-1 RNA levels > 5000 copies/ml. Escalating doses of 50, 100 or 200 mg dexelvucitabine were administered. Dexelvucitabine demonstrated potent antiviral activity, with a mean decrease in HIV RNA at the end of treatment of 1.77 ± 0.23 $\log_{10}$ copies/ml for the highest dose. The C_{max} values at all doses exceeded the *in vitro* EC_{90} for wild-type HIV-1, and the C_{max} at the highest dose (9.8 ± 2.9 μM) exceeded the EC_{90} for mutant (M184V and K65R) HIV-1. Dexelvucitabine was well tolerated; there were no serious adverse events and no dose-limiting toxicity (25).

The tolerance and anti-HIV-1 activity of dexelvucitabine were evaluated in another 10-day study in 10 treatment-experienced HIV-infected individuals. Dexelvucitabine 200 mg or placebo was added to the current failing regimen. The mean decrease in viral load at the end of the study was 0.8 $\log_{10}$ copies/ml and activity was demonstrated in subjects with virus harboring mutations resistant to zidovudine and/or lamivudine. No serious adverse events were reported and all adverse events were mild or moderate in severity (26).

The randomized, double-blind, placebo-controlled phase IIb RVT-203 study was conducted in 199 treatment-experienced patients who were viremic on their current regimen. The study was conducted in 3 phases: a 2-week add-on phase during which patients received dexelvucitabine 50, 100 or 200 mg once daily or placebo, a 14-week optimized treatment phase, and an 8-week safety phase during which patients randomized to placebo could switch to active treatment. Antiviral activity after the 2-week add-on phase was shown by a decrease in mean viral load of 0.7 $\log_{10}$ copies/ml for the highest dose. At 16 weeks, there was a 54% overall response, defined as a decrease in viral load of at least 1.0 $\log_{10}$ copies/ml, and a mean decrease in viral load of 1.2 $\log_{10}$ copies/ml for the highest dose. Adverse events were generally mild and included headache, fatigue and gastrointestinal disorders. Pancreatitis and asymptomatic hyperlipasemia were observed when dexelvucitabine was administered with didanosine, leading to the recommendation that the compounds not be used in combination. The events resolved on cessation of treatment. No novel mutations were observed in dexelvucitabine-exposed patients (27, 28).

The FDA has requested that a further phase II trial be conducted to confirm the efficacy and safety data from the above study before it will approve advancement into phase III trials (29).

Sources

Originated at Emory University, Atlanta GA (US); licensed to Pharmasset, Inc. (US); sub-licensed and codeveloped with Incyte Corp. (US).

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