Le Infezioni in Medicina, n. 4, 495-499, 2023
doi: 10.53854/liim-3104-8

Pharmacological outlook of Lenacapavir: a novel first-in-class Long-Acting HIV-1 Capsid Inhibitor

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Article received 14 October 2023, accepted 16 November 2023

SUMMARY

The evolution of antiretroviral therapy is now addressed to develop regimens consisting of two instead of three drugs and it is also increasingly oriented to develop long-acting parenteral formulations in order to increase treatment adherence and to reduce the multifaceted individual burden associated to daily intake of drugs. This new way was first paved by the dual association consisting of the INSTI Cabotegravir and the NNRTI Rilpivirine, whose formulations allow for a single administration every two months. In 2022 a new drug with a novel mechanism of action and a longer persistence of effective drug concentrations was made available in many countries for the treatment of drug-resistant HIV infection in association to other antiretrovirals. Lenacapavir is a first in class capsid inhibitor that exerts its inhibitory effect on HIV replication by binding to a structural protein of the capsid. This unprecedented mechanism of action actually differs from those of all prior antiretrovirals as Lenacapavir interferes with multiple stages rather than with a single enzyme. Such binding determines a series of inhibitory effects on sequential steps of the HIV life cycle and the net result is that of an impressive intrinsic antiretroviral potency, as testified both by *in vitro* studies and the 10-day monotherapy clinical study with single injections. The antiretroviral activity of Lenacapavir is unaffected by any mutation conferring resistance to older antiretrovirals. Lenacapavir is slowly released from the site of injection and this requires an initial coverage by its oral formulation (half-life: 10-12 days) in order to provide adequate pharmacokinetic exposure in the first days of treatment. The subcutaneous administration of Lenacapavir (half-life: 8-12 weeks) is then scheduled every 6 months. Lenacapavir is metabolized by CYP3A and UGT1A1, it is a substrate of Pgp and a moderate inhibitor of CYP3A. While co-administration with strong inducers of these enzymatic entities is contraindicated or it is not recommended in case of weaker inducers, few are the potential interactions of Lenacapavir as perpetrator (by its moderate inhibitory effect on CYP and weak inhibition of Pgp). In most such cases no preventive dosage adjustments are recommended and clinical monitoring only is advised. Lenacapavir overall characteristics thus meet the major clinical-pharmacologic expectations of this new era of antiretroviral development. A safe and truly potent antiviral drug, with a low metabolic interactive potential and a frequency of administration with the potential to be successfully employed beyond the current therapeutic indications.

Keywords: Pharmacology, HIV, capsid inhibitors, Lenacapavir.

INTRODUCTION

In 2021 the first long-acting injectable option for the treatment of HIV infection, such as the dual combination consisting of a strand-transfer integrase inhibitor (INSTI), Cabotegravir (CAB), and of the non-nucleoside reverse transcriptase inhibitor Rilpivirine (RPV), was approved for clinical use [1]. CAB was also approved as single long-acting agent for pre-exposure prophylaxis (PrEP) in 2022 [2]. I 2022 a further long-acting agent, Lenacapavir, received first approval in the EU for the treatment of drug-resistant HIV infection in combination with other antiretrovirals when no other suitable options are available [3]. Lenacapavir is a

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first-in-class capsid inhibitor with a unique multi-stage mechanism of action that was developed both as oral agent and injectable long-acting formulation [4]. The drug is initially given as oral agent and then it is administered subcutaneously (sc) with dosing intervals of 6 months. As it was in the case of CAB – RPV, for which an oral lead-in phase is also scheduled, the release of these new injectable long-acting compounds has challenged our clinical-pharmacological knowledge for several good reasons. While in the case of oral drugs we became accustomed to manage issues like drug-drug interactions, forgiveness (unscheduled interruption of drug intake) as well as appropriate timing for switching to new regimens, with these new injectable long-acting antiretrovirals we have to face new potential uncertainties resulting from both the prolonged persistence of measurable drug levels following a single injection and the unusual route of administration, such as the fact that injectable drugs skip the intestinal absorption and their release into circulation is not influenced by hepatic first-pass metabolism [5-7].

PHARMACODYNAMICS OF LENACAPAVIR

Mechanisms of action

The mechanism of action is unprecedented among all antiretrovirals so far developed, as the drug actually interferes in multiple steps of HIV replication cycle. Lenacapavir is a molecule of 968.28 $g \cdot mol^{-1}$ that is classified as HIV capsid inhibitor. Its multistage inhibition entails the process of selective binding to the interface between capsid subunits and such interaction determines the inhibition of capsid-mediated nuclear uptake of HIV-1 proviral DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of CA subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to irregularly formed capsids) [4]. Lenacapavir thus does not bind to enzymes involved in the replication cycle of the virus but to a structural component of the virus, such as the capsid protein. The latter is made by hexamers and pentamers and provides a protective envelope to the genetic material of the virus [8]. The first action of Lenacapavir in the sequential steps of the viral replication cycle consists of the inhibition of the transfer of viral cDNA into the nucleus which results in a reduced integration of proviral DNA. In addition Lenacapavir increases the strength of intra- and extrahexamer interactions that leads to faster assembly of capsid monomers into an aberrant form with reduced infectivity.

The *in vitro* intrinsic antiviral potency of Lenacapavir was determined in lymphoblastoid cell lines, primary monocyte/macrophage cells, PBMC and CD4+ T-lymphocytes, with resulting EC_{50} (half-maximum effective concentration) ranging from 30 to 190 pM (mean EC_{50} 105 pM/L). These values unambiguously identify Lenacapavir as one of the most potent drug among antiretrovirals [9]. The antiretroviral activity of Lenacapavir was challenged against viral isolates resistant to the main existing antiretroviral drug classes, such as nucleoside/nucleotide and non-nucleoside reverse transcriptase inhibitors (NtRTIs, NNRTIs), protease inhibitors (PIs), strand-transfer integrase inhibitors (INSTIs) and entry inhibitors (EIs), with no reduction of activity. This demonstrates the fully independent mechanisms of action of the drug from those of older antiretrovirals. The same applies to the naturally occurring Gag polymorphisms of HIV-1 [10].

A common clinical experiment included in antiretroviral development is the measurement of viral load decrease in a 10-day time following administration of the drug alone, such as without any companion drugs. This allows for indirect comparison of *in vivo* intrinsic antiviral potency of antiretrovirals and in the case of Lenacapavir, given its long elimination half-life, HIV-RNA was measured after single injections of different doses of the drug. Mean viral load decreases ranged from -1.4 $\log_{10}$ to -2.3_{10} in a dose-proportional manner, such as the greatest dose injected (750 mg) determined the maximum effect [11]. Such decrease is of the same order of magnitude of the one achieved by INSTIs in similar experiments and it further testifies of the remarkable antiretroviral potency of Lenacapavir [12].

PHARMACOKINETICS

Lenacapavir pharmacokinetics following a single oral dose was found to be non-linear and less than dose-proportional with doses ranging from 50 to 1800 mg, while in case of subcutaneous injection dose-proportionality was seen with doses ranging

from 309 to 927 mg [13, 14]. The median half-life following oral and subcutaneous administration ranged from 10 to 12 days, and 8 to 12 weeks, respectively. Oral Lenacapavir has a bioavailability of 6-10%, and the peak of maximum concentration is measured after 4 hours. Subcutaneous Lenacapavir is completely absorbed and slowly released from the site of injection with peak plasma concentration taking place 84 days following administration. Plasma concentrations remains well above the response cutoff for more than 6 months after a single dose of 900 mg administered subcutaneously, but due to the slow initial diffusion into circulation oral Lenacapavir is administerd for an initial loading phase. The volume of distribution of Lenacapavir is 976 L, as calculated from a population-Pk study and the drug is 99.8% bound to protein. From the population-Pk analyses based on findings from clinical trials no relevant differences were found attributable to age, gender, ethnic factors or body weight [13, 14].

In patients with moderate hepatic impairment (Child group B) the Pk exposure of Lenacapavir was found to be 1.47 to 2.84 fold and 2.61 to 5.03 higher (AUC and Cmax, respectively) when compared to subjects with normal liver function, but such increases are not considered to be of clinical relevance [1]).

In patients with severe renal impairment (CrCl ≥ 15 and ≤30 mL/min) an oral dose of 300 mg led to an increase of 84% and 162% (AUC and Cmax, respectively) as compared to subjects with normal renal function, but these increases are not considered of any clinical relevance [16]. Since the drug is 99.8% bound to protein the dialysis is not expected to modify the Pk exposure of Lenacapavir [17].

METABOLISM

Lenacapavir is metabolized by the isoenzyme CYP3A of the cytochrome P450 system and through glurcuronidation by the uridin diphosphate glucuronosyltransferase 1A1 (UGT1A1) [17].

It does not induce CYP3A and may act as weak inhibitor on the same enzymatic unit. The drug is a substrate of the P-glycoprotein (Pgp) membrane transporter, with no modulating effect on Pgp itself, BCRP (breast cancer resistant protein) and OAT (organic anion transporter). Lenacapavir is mainly cleared by the biliary route, as seen with a single injection of radiolabelled drug; 76% of radioactive Lenacapavir was found in faeces and less than 1% in the urine. Unchanged lenacapavir was the predominant moiety in plasma (69%) and feces (33%) [17].

Drug – drug interactions

Metabolic interactions of Lenacapavir have been mostly investigated with the oral 300 mg dose and more data from phase IV evaluation are expected about the interactive potential of the subcutaneous formulation of the drug. Such a distinction should be considered as parenterally administered drug avoid the first-pass metabolism.

Inducers or inhibitors of CYP3A and UGT1A1 may determine variations in the plasma exposure of Lenacapavir. Drugs known to exert significant induction of CYP3A and UGT1A1 like rifampicin, the anticonvulsants carbamazepine, phenytoin and the herbal product St. John's wort (Hypericum perforatum) are contraindicated due to the significant reduction in Pk exposure of Lenacapavir. Caution should be exercised also in introducing Lenacapavir following cessation of such strong inducers, as their action persists for weeks after discontinuation and an interval of at least 4 weeks is recommended. Moderate inducers of CYP3A may also determine reductions of Lenacapavir Pk exposure and this applies to antiretrovirals like Efavirenz, Nevirapine, Etravirine and Tipranavir / Ritonavir that are therefore not recommended [18].

Concomitant inhibition of CYP3A, Pgp and UGT1A1 as it occurs with Atazanavir/Cobicistat may significantly increase the Pk exposure of Lenacapavir and should not be administered (not recommended), while inhibition of CYP3A only, like in the case of Voriconazole, is associated to clinically irrelevant increases in Lenacapavir Pk xposure (AUC and Cmax increased by 41% and 9% respectively). Even in the case of Darunavir/Cobicistat, whose inhibitory action involves both CYP3A and Pgp, the PK changes are not considered to be of clinical relevance (AUC and Cmax increased by 94% and 130%, respectively) [19].

Looking at Lenacapavir as a possible perpetrator of drug-drug interactions, the relevant metabolic pathways of interest are the moderate inhibition of CYP3A and the weak inhibition of Pgp by Lenacapavir. Caution should be applied in case of drugs with a narrow therapeutic index. Substrates of some concern here are dihydroergotamine, ergotamine, sildenafil, vardenafil, systemic dexametha-

sone or hydrocortisone/cortisone, lovastatin, simvastatin, digoxin, midazolam, triazolam, rivaroxaban, dabigatran, edoxaban [19]. Due to the persistence of Lenacapavir concentrations for prolonged periods, the inhibitory effects of the drug might still impact on the Pk exposure of these substrates within 9 months following the last injection of Lenacapavir.
No restrictions emerged for Lenacapavir co-administration with drugs that are substrates of BCRP, Pgp alone, OATP and the same applies for acid-reducing agents [19].
A more general view of the low metabolic interactive potential of Lenacapavir is provided by matching it with the 20 most commonly prescribed drugs in Italy as of December 2022 [20, 21]. Only 4 drugs out of 20 listed showed some degree of possible clinically meaningful interactions, all resulting from CYP3A inhibition by Lenacapavir. Two statins, Rosuvastatin (AUC and Cmax increased by 31% and 57%, respectively) and Atorvastatin and the b-blocker Bisoprol are considered to have a weak potential for overexposure when co-administered with Lenacapavir. The anti-hypertensive Amlodipine is classified as possible victim of potential interaction. In all such cases no preventive dose adjustments are recommended and only clinical monitoring is advised [21].

CONCLUSIONS

The novelties of the last few years in antiretroviral chemotherapy not only consist of new drugs, but also of newer routes of administration allowing less frequent dosing due to the long-lasting persistence of effective drug concentrations. Following the release of CAB – RPV as new option for maintenance therapy in virologically suppressed patients [1], the capsid inhibitor Lenacapavir has been successfully developed for the treatment of drug-resistant HIV infection and is now available in many countries [22]. Lenacapavir has a totally new mechanism of action and no pre-existing viral mutations selected by older drugs were found to impact on Lenacapavir antiretroviral activity. From a pharmacodynamic viewpoint the major interest on Lenacapavir lies in the fact that its selective binding to capsid proteins has multiple inhibitory downstream effects on the HIV replication cycle. Thus instead of the inhibition of a single enzymatic activity involved in HIV replication, Lenacapavir action impacts on several sequential steps and not surprisingly this corresponds to one of the greatest intrinsic antiretroviral potency ever recorded in HIV pharmacology. Such action on multiple development steps is reminiscent of other anti-infective drugs like artemisinin derivatives devised for the treatment of malaria and the NS5a inhibitors for HCV infection [23, 24]. In both such cases their introduction in therapy led to unprecedented advances in the treatment of both diseases. And this is likely to be the case also for Lenacapavir as its properties make it an ideal candidate not only for the currently approved indication but in a foreseen future as part of maintenance regimens in virologically suppressed patients. Lenacapavir overall profile well fits with the current era of antiretroviral therapy not only in terms of intrinsic antiviral properties but also looking at its tolerability and safety as well as at its metabolic characteristics. The latter aspect is critically important as the drug, once injected, will remain for a prolonged time in the body and the intake of other drugs in combination must be devoid of significant drug-drug interactions. Lenacapavir significantly meets this requirement since with few exceptions its metabolism is compatible with the vast majority of most commonly used medications. The future prospect of antiretroviral therapy is increasingly oriented toward dual regimens and injectable long-acting formulations. In this view newer drugs are expected to exert strong antiretroviral action to compensate for the lack of a third drug, to be available as parenteral long-acting formulations and to minimize the risk of drug-drug interactions. Lenacapavir has all such properties.

Conflict of interest
Giovanni Di Perri has received research grants from Gilead Sciences, ViiV, MSD, fees for consultancies and for lectures from Abbvie, Gilead Sciences, MSD, ViiV, Janssen, Pfizer, Astra-Zeneca, Roche.

Funding
None

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