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HIGHLIGHT

Sunlenca® (Lenacapavir): A first-in-class, long-acting HIV-1 capsid inhibitor for treating highly multidrug-resistant HIV-1 infection

KEY WORDS

Lenacapavir;
Capsid inhibitor;
HIV-1 infection;
HIV prevention;
Multidrug resistance;
Antiretroviral medication

Lenacapavir, also known as GS-6207, under the brand name Sunlenca, was developed by Gilead Sciences Inc. It has been approved in the EU, Canada, and US for use alongside other antiretrovirals in adults with multidrug-resistant HIV infection and those who cannot otherwise establish an effective antiviral treatment regimen (Fig. 1)[1,2]. The US Food and Drug Administration (FDA) approval is mainly based on the result of the phase II/III CAPELLA trial (NCT04150068)[2]. In the lenacapavir group, over 80% of patients with multidrug-resistant HIV-1 had fewer than 50 viral RNA copies per milliliter by week 26, and no serious adverse events related to the drug were reported[3,4]. According to the results of the phase III PURPOSE-1 study (NCT04994509), Gilead Sciences recently revealed that administering lenacapavir subcutaneously every 6 months showed 100% effectiveness in preventing HIV infections in cisgender women. This approach outperformed Truvada (200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate; F/TDF) taken orally on a daily basis, considering both efficacy and the prevailing HIV incidence rates.

Distinct from other approved antiretroviral drugs, lenacapavir inhibits HIV-1 by targeting the function of HIV-1 capsid protein (p24, abbreviated as CA). It tightly binds two adjacent capsid subunits to accelerate the subunit assembly, leading to the generation of malformed CA with higher stability than uncombined particles[5]. Through which it inhibits functional disassembly of the capsid shell and interferes with the interactions between CA and proteins that are indispensable for the HIV-1 replication cycle[6]. For example, lenacapavir remarkably reduces the binding of CA and host-cell nuclear import cofactors (NUP153 and CPSF6), thereby blocking the nuclear import and integration of HIV-1 cDNA. Lenacapavir exhibits substantial antiviral activity against various subtypes of HIV-1 in human cell lines and primary cells with picomolar mean EC_{50}. Moreover, it shows excellent *in vitro* safety with a selectivity index of more than 10^6. Notably, the drug displays sub-nanomolar potency against a variety of HIV-1 variants that are resistant to nucleotide emtricitabine (reverse transcriptase inhibitor), efavirenz (nonnucleotide reverse transcriptase inhibitor), elvitegravir (integrase strand transfer inhibitor), or atazanavir (protease inhibitor), making this drug a transformative arsenal to treat multidrug-resistant HIV infections. The superior anti-resistance of this drug is attributed to the unique mechanisms of action.

In the phase I clinical study, subcutaneous lenacapavir exhibited favorable pharmacokinetic properties in healthy volunteers[5]. A dose-proportional increase in AUC and C_{max} was observed, reaching 10,800 h ng/mL and 58.4 ng/mL, respectively, at a dose of 450 mg. Surprisingly, T_{max} ranged from 14 to 35 days across different doses, indicating a slow-release kinetic possibly attributed to the compound's high lipid solubility. Moreover, $T_{1/2}$ of the 30, 100, 300, and 450 mg doses were between 31.9 and 45.4 days, demonstrating high metabolic stability in humans. At a single dose of $\geq$300 mg, lenacapavir maintained plasma exposure levels exceeding the concentrations needed for anti-HIV activity for over 24 weeks. This supports its twice-yearly administration in the phase III PURPOSE-1 study. The low hepatic clearance is a key factor in the design and development of this drug. Three

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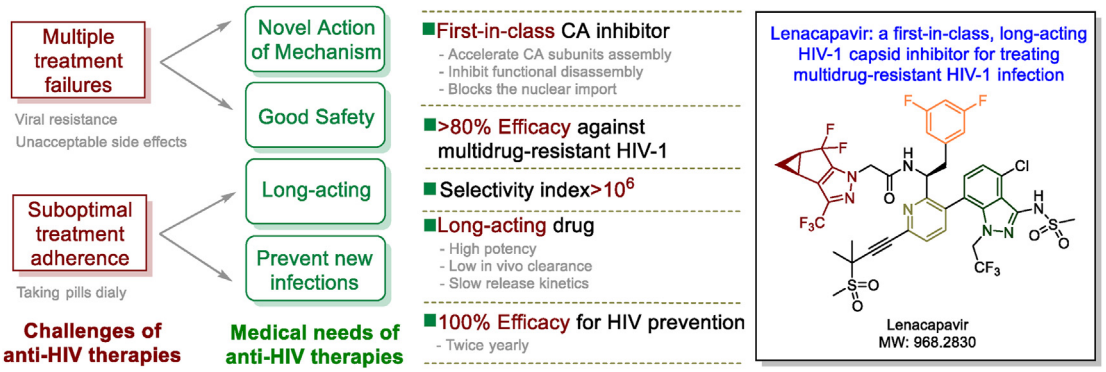

Figure 1 Lenacapavir, a first-in-class and long-acting HIV-1 capsid inhibitor for HIV-1 treatment.

strategies were employed to block metabolically labile sites: (i) incorporating electron-withdrawing groups, including ten fluorine atoms, one chlorine atom, and two sulfonyl groups; (ii) introduction of metabolically stable ring systems (two pyrazoles and one cyclopropane); (iii) increasing the rigidity of the molecule (fused bicyclic group, fused tricyclic group, alkynyl group). Altogether, the picomolar-level antiviral activity, slow-release kinetics, and high *in vivo* metabolic stability make lenacapavir a long-acting anti-HIV agent.

Link et al.[5] and Bester et al.[6] independently determined the X-ray crystal structures of lenacapavir bound to the CA hexamer (PDB ID: 6V2F and 6VKV) to reveal how the drug interacts with CA at a molecular level[5,6]. It exhibits extensive interactions and notable shape complementarity with the hydrophobic cavity formed by two adjacent CA monomers. The 3,5-difluorobenzene ring and cyclopentapyrazole group strongly interact *via* van der Waals forces with the N-terminal domain of CA subunit 1 (CA1-NTD) and the C-terminal domain of CA subunit 2 (CA2-CTD). The pyridine and indazole rings also interact hydrophobically with the CA1-NTD and N-terminal domain of CA subunit 2 (CA2-NTD). The methane sulfonamide group in lenacapavir forms a hydrogen-bonding network that connects the side chains of Lys70 and Asn74 in CA1-NTD to Gln179 and Asn183 in CA2-CTD. The methyl sulfonyl group forms an additional hydrogen-bonding network with the side chains of Asn57 in CA1-NTD and Ser41 in CA2-NTD. Additionally, the amide and pyridine group form three hydrogen-bonding interactions with the side chains of Asn57 and Lys70. Based on these tight binding modes, lenacapavir could be seen as a molecular glue that speeds up the assembly of CA monomers and stops the capsid shell from disassembling functionally.

Lenacapavir represents a groundbreaking advancement in the treatment and prevention of HIV-1 infection. It possesses key characteristics of ideal antiretroviral drugs: long-lasting effects, strong antiviral activity against drug-resistant strains, favorable pharmacokinetics, excellent safety profiles, and integration for both therapeutic and prophylactic purposes. The success of lenacapavir offers insights into new drug discovery and development. Apart from similar interactions with CA1-NTD, lenacapavir engages in more extensive hydrophobic and hydrogen-bonding interactions with the adjacent CA2 compared to the less potent inhibitor PF-3450074[6], indicating that establishing a hydrogen-bonding network bridges both proteins, and sufficient hydrophobic interactions benefit the development of drugs targeting protein−protein interactions. The favorable pharmacokinetic properties of this drug, with a molecular weight (MW) of 968.3 and high lipid solubility, open up new possibilities for the development of drugs beyond the Rule of Five (Ro5), particularly PROteolysis TArgeting Chimeras (PROTACs) and macrocyclic drugs. The high lipid solubility could hinder *in vivo* absorption, but it can also provide the compound with slow and sustained release kinetics when administered *via* subcutaneous injection. This is a crucial feature of a long-acting drug. Compared to the predecessor inhibitor GS-A1, lenacapavir, with the incorporation of two fluorine atoms, shows improved metabolic stability and potency[7,8], showing the "magic" fluorine effect in drugs, particularly those with a molecular weight greater than 500 Da.

While lenacapavir is effective and well-tolerated for treating and preventing HIV-1 infection, resistant mutations in the CA region may develop over time, leading to reduced drug susceptibility[9,10]. For example, the M66I mutation decreases antiviral effectiveness of lenacapavir by over 84,000 times. Thus, there is an urgent medical necessity to develop a second-generation HIV-1 capsid inhibitor. Furthermore, the success of lenacapavir opens up possibilities for long-term treatment and prevention of other infectious diseases caused by viruses with capsid proteins, such as hepatitis B virus, norovirus, and dengue virus.

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Author contributions

Bin Yu conceived the idea. Chunhua Ma wrote the draft manuscript. Junbiao Chang and Bin Yu revised the manuscript. All authors have read and approved submission of the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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