Review

Bevirimat: a novel maturation inhibitor for the treatment of HIV-1 infection

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Existing antiretroviral treatments for HIV type-1 (HIV-1) disease are limited by problems of resistance and drug–drug interactions. Bevirimat is a novel HIV-1 maturation inhibitor with a mechanism of action that is distinct from other antiretroviral agents. Specific inhibition of the final rate-limiting step in Gag processing by bevirimat prevents release of mature capsid protein from its precursor (CA-SP1), resulting in the production of immature, non-infectious virus particles. Bevirimat inhibits replication of both wild-type and drug-resistant HIV-1 isolates in vitro, achieving similar 50% inhibitory concentration values with both categories. Serial drug passage studies have identified six single amino acid substitutions that independently confer bevirimat resistance. These resistance mutations occur at or near the CA-SP1 cleavage site, which is not a known target for resistance to other antiretroviral drugs. Bevirimat has demonstrated a consistent pharmacokinetic profile in healthy volunteers and HIV-infected patients, with peak plasma concentrations attained approximately 1–3 h after dosing. Plasma concentrations decrease in a log-linear manner with a mean plasma elimination half-life of 58–80 h, supporting once-daily dosing. Animal studies suggest that elimination of bevirimat is primarily by hepatic glucuronidation and hepatobiliary excretion. There is minimal renal elimination, with <1% of the administered dose appearing in the urine. In responsive patients, bevirimat has demonstrated a robust dose-dependent reduction in viral load (>1.5 log10 copies/ml). Short-term administration (≤14 days) of bevirimat is well tolerated, even when used in combination with other antiretroviral agents. Further studies to evaluate the long-term efficacy and tolerability of bevirimat are currently underway.

Introduction

HIV/AIDS continues to spread globally and remains a major health crisis affecting more than 40 million people worldwide [1]. HIV infection is a chronic but treatable disease. Highly active antiretroviral therapy (HAART) combines antiretroviral therapies with different modes of action and has markedly improved the prognosis of patients infected with HIV. However, patients are increasingly affected by the long-term side effects of antiretroviral therapy [2], drug toxicity and drug–drug interactions, all of which could adversely affect treatment options and outcome. Therefore, there is a need for new antiretrovirals with improved tolerability and safety profiles [2,3].

Consequently, many patients who achieve undetectable plasma HIV type-1 (HIV-1) RNA levels following treatment ultimately experience treatment failure owing to the development of antiretroviral resistance [4–6]. In addition, cross-resistance among existing antiretrovirals limits the available options for salvage therapy, particularly in patients who have experienced multiple episodes of virological failure [2,5–7].

Primary infection with antiretroviral-resistant HIV-1 has become an important clinical problem in many regions, including the USA and western Europe, rendering available treatments less effective [8–10]. For example, in areas where antiretroviral therapy is widely used, such as the USA and Canada, 8–12% of new HIV-1 infections involve viruses resistant to one or more approved drugs [11,12]. Therefore, there is also a need for new antiretrovirals with novel mechanisms of action, which will not be subject to cross-resistance with existing agents [13].
Several new classes of antiviral agents are under development [14,15] including those that target cellular receptors involved in HIV binding and other components of the HIV virus. One of the most promising novel approaches is to target maturation of new viruses by blocking the Gag protein processing, via direct interaction of the drug with the Gag molecule, rather than the protease. Examples of such an approach are the peptide glycyl-prolyl-glycine-amide [16] and the small molecule drug, bevirimat.

Beverimat is a novel HIV-1 maturation inhibitor with a mode and site of action that is distinct from other approved antiretroviral agents [17–19] and has limited potential for cross-resistance typically seen with existing agents [13,20]. As the first maturation inhibitor in clinical development for the treatment of patients with HIV-1 infection, bevirimat interrupts the last step in viral maturation and prevents the new viruses from becoming infectious [17–19,21]. This paper reviews the biochemical, virological and pharmacokinetic properties of bevirimat, together with its clinical efficacy and tolerability in HIV-infected patients.

Chemical structure and mechanism of action

Beverimat (3-O-[3′,3′-dimethylsuccinyl] betulinic acid [PA-457]; Panacos Pharmaceuticals Inc., Watertown, MA, USA) is a derivative of aliphatic triterpenic acid with two carboxyl groups (Figure 1) [17]. Bevirimat was developed following activity-directed derivatization of betulinic acid, which had been originally identified as a weak inhibitor (therapeutic index <5) of HIV-1 replication [22,23].

Beverimat blocks HIV-1 maturation and subsequently disrupts virus infectivity via a mechanism of action distinct from that of any other class of antiretrovirals (Figure 2) [21]. Unlike protease inhibitors (PI), bevirimat exerts its action on the Gag substrate rather than the protease enzyme. As a specific inhibitor of the final rate-limiting step in Gag processing, bevirimat prevents the release of mature capsid protein (capsid [CA] or p24) from its precursor (capsid spacer peptide 1 [CA-SP1] or p25, also referred to as CA-p2) [17–19,21,24]. Bevirimat enters a nascent virion as it buds from an infected cell and binds to the Gag polypeptide at the CA-SP1 junction, preventing the protease enzyme from cleaving CA-SP1. As the capsid protein remains tethered to SP1, the virion core is prevented from assuming its normal conical shape crucial for infectivity, resulting in the release of immature, non-infectious virus particles [17–19,21]. These virus particles display an electron-dense layer of Gag adjacent to the viral membrane [17]. The amino acid residues in the N-terminal half of the SP1 appear to serve as the major determinants of bevirimat activity, whereas residues in the C-terminal half of SP1 might play a lesser role in compound activity [24]. Such findings identify the CA-SP1 domain as the primary viral determinant for this novel inhibitor of HIV-1 replication.

In vitro virological activity

Antiretroviral activity

Beverimat has demonstrated the ability to inhibit replication of both wild-type and drug-resistant HIV-1 isolates [17]. As a potent inhibitor of HIV-1 replication in vitro, activity of bevirimat varies approximately 10-fold against different clades, while achieving 50% inhibitory concentration (IC$_{50}$) values in the nM range [17]. For example, bevirimat demonstrates activity against wild-type HIV-1 similar to that...
of currently approved nucleoside analogue reverse transcriptase inhibitors (NRTIs) and PIs, inhibiting wild-type HIV-1 with a mean IC_{50} of 10.3 nM [17]. In addition, this activity was retained against virus isolates resistant to approved NRTIs and PIs, with a similar mean IC_{50} (7.8 nM) to that observed against drug-sensitive HIV-1 strains. Such potency of suppression against drug-sensitive HIV-1 strains. Such potency of suppression residues of the N-terminal SP1 (A364V, A366T and respectively) and three positioned at the first and third residues of the N-terminal SP1 (A364V, A366T and A366V, also referred to as SP1-A3V, SP1-A3T and SP1-A3V, respectively) within the CA-SP1 boundary domain [17,19,27]; SP1-A1V appears to arise most frequently [27]. Of these mutations, CA-H226Y, CA-L231F, CA-L231M and SP1-A1V do not appear to exert a significant replication defect on the HIV-1 virus in vitro, whereas the mutations SP1-A3V and SP1-A3T severely impair virus replication and inhibit virion core condensation [27]. Second-site mutations were readily acquired by SP1-A3V, which could compensate for the replication defect imposed by SP1-A3V. Sequences from PI-experienced patients with HIV-1 subtype B have been assessed for the presence of resistance mutations to bevirimat [28]. Overall, the CA-SP1 cleavage site was highly conserved in PI-pretreated patients and the presence of mutations appeared infrequent, with only one patient displaying a CA-L231M mutation. Such findings suggest that bevirimat could be used successfully in PI-experienced patients.

The CA-SP1 cleavage site is the target for all identified mutations conferring bevirimat resistance, however, this region of Gag is not known to be a target for resistance to other antiretrovirals, including PIs [17,27,29]. Such findings suggest that bevirimat-resistant viruses should retain susceptibility to all other approved and known investigational classes of antiretroviral therapy. This is supported by laboratory experiments where the majority of approved antiretrovirals tested had a fold change in susceptibility of <1 when comparing wild-type virus with bevirimat-resistant HIV-1 with the A364V mutation [27]. Using a panel of reverse transcriptase, protease and fusion inhibitor-resistant HIV-1 isolates, Kilgore et al. [30] have demonstrated that bevirimat is a potent in vitro inhibitor of such isolates and retained wild-type activity, whereas comparator drugs exhibited decreases in activity ranging from several-fold to >100-fold [30].

**Pharmacokinetics**

**Clinical pharmacokinetics**

Animal studies have demonstrated that bevirimat is rapidly absorbed after intravenous or oral administration and is widely distributed into peripheral tissues, including potential sanctuary sites for HIV infection [31]. Bevirimat has also shown a consistent pharmacokinetic profile in studies in healthy human volunteers [32,33] and HIV-infected patients [34].

Bevirimat demonstrated largely linear pharmacokinetics following oral administration of single doses (25, 50, 100 and 250 mg) in healthy adult volunteers [32]. Bevirimat was rapidly absorbed after oral administration, with detectable concentrations present in the plasma within 15 min after administration and peak plasma concentrations being attained approximately 1–3 h after dosing (Table 1). Plasma concentrations decreased in a log-linear manner with a mean plasma elimination half-life ranging from 58 to 80 h; the long half-life of bevirimat supports once-daily dosing.
Multiple-dose pharmacokinetics appear consistent with those seen after single doses [33,35]. Similarly, values for pharmacokinetic variables in HIV-positive patients appear comparable with those of bevirimat reported in healthy volunteers [34]. Plasma concentrations of bevirimat were only modestly decreased in a dose-dependent manner when coadministered with ritonavir [36] and minimal pharmacokinetic differences were noted for either atazanavir or bevirimat when used in combination (Table 2) [37]. Consequently, it should not be necessary to adjust the bevirimat dose when it is used in conjunction with other treatments. Elimination of bevirimat is primarily via hepatic biliary routes [31] with renal elimination accounting for <1% of the administered dose [31,32]. These findings suggest that bevirimat has a low potential for interaction with currently approved therapies and is, therefore, a potentially valuable addition to HAART regimens.

Intracellular pharmacokinetics

Bevirimat is not oxidatively metabolized by human liver microsomes and does not inhibit the cytochrome P450 system or interact with human P-glycoprotein [38] Bevirimat is eliminated primarily by hepatic glucuronidation, largely by the UGT1A3 isofom and, to a lesser extent, by the UGT2B7 and UGT1A4 isoforms [31,39,40]. Acyl glucuronide metabolites of bevirimat (including two mono-glucuronides [mono-BVMG (I) and mono-BVMG (II)] and one di-glucuronide [di-BVMG]) appear relatively stable, reducing the likelihood that they might act as reactive intermediates [39]. The plasma concentration of these metabolites represents <1% of the administered dose [32]. In addition, bevirimat shows limited or no interactions via glucuronidation with other antiretrovirals tested [36,37]. Although atazanavir can cause hyperbilirubinaemia resulting from inhibition of bilirubin glucuronidation by UGT1A1, bevirimat does not increase bilirubin levels [37]. Of particular note, bevirimat does not significantly induce cytochrome P450 3A4, which is commonly involved in the metabolism of PIs and non-nucleoside reverse transcriptase inhibitors [33].

Clinical efficacy

A double-blind, placebo-controlled study in 32 HIV-1-infected patients (median viral load at entry,
4.73 log_{10} copies/ml demonstrated that oral bevirimat once daily for 10 days (placebo, 25, 50, 100 or 200 mg) can decrease HIV-1 viral load. Significant reductions in median viral load at day 11 were seen in patients receiving 100 or 200 mg bevirimat with decreases of 0.48 log_{10} copies/ml (67%, \( P=0.0036 \)) and 1.03 log_{10} (91%, \( P<0.0001 \)), respectively. Viral load was reduced by \( \leq 1.7 \log_{10} \) copies/ml in individual patients [41]. A further study investigating the efficacy of higher doses of bevirimat as functional monotherapy in patients with documented resistance to approved drugs is ongoing.

Safety and tolerability

Preclinical

To date, preclinical exposure has not provided any indication that bevirimat might be associated with any specific safety concerns that could limit its clinical use. \textit{In vitro} preclinical studies in human cells suggest that an agent such as bevirimat should have a low potential for cytotoxicity, including cardiotoxicity [42]. In addition, there is no evidence of any reproductive or developmental toxicity with bevirimat and it is not immunotoxic (unpublished data).

Clinical

Short-term administration (\( \leq 14 \) days) with bevirimat was well tolerated, even with multiple doses, during pharmacokinetic studies in healthy volunteers [32,33,43]. In addition, no dose-limiting toxicities or serious adverse events were reported [32,33]. Similarly, the use of bevirimat in HIV-1-infected patients was well tolerated at all studied doses (\( \leq 230 \) mg) with no significant treatment-related adverse effects, no dose-limiting toxicities, no serious adverse events and no deaths reported [34,43]. Changes in CD4+ T-cell counts did not vary significantly between bevirimat doses [34]. Such findings suggest that bevirimat has a tolerability and safety profile that appears to be suitable for long-term dosing. Of noteworthy interest, long-term use of bevirimat in a lower-exposure solid dosage formulation has revealed no safety concerns after 4 months of dosing (unpublished data).

Pharmacokinetic and pharmacodynamic interactions between antiretrovirals, and between antiretrovirals and other medications, are an important consideration for the choice of therapy in both clinical practice and drug development. As antiretroviral agents could be coprescribed with bevirimat as part of a HAART regimen, the tolerability and safety of such combinations is important. Bevirimat has currently demonstrated good tolerability and safety when administered in combination with ritonavir or atazanavir in healthy individuals, with all treatment-emergent adverse events being mild or moderate in nature and resolved prior to study end [36,37]; no serious adverse events or deaths were reported. Additional studies of the use of bevirimat in combination with other antiretrovirals are underway.

Conclusions

Bevirimat is a novel maturation inhibitor with a mode of action distinct from other antiretroviral agents. Bevirimat is effective across the spectrum of HIV-1 disease and inhibits replication of both wild-type and drug-resistant HIV-1 isolates, with activity varying approximately 10-fold against different clades and \( IC_{50} \) values in the nM range. \textit{In vitro} studies demonstrate that bevirimat exhibits no cross-resistance with other antiretroviral classes and bevirimat-resistant viruses retain susceptibility to all other approved and investigational classes of antiretroviral therapy. In HIV-1-infected patients, bevirimat oral therapy results in clinically significant reductions in viral load and this reduction appears to be dose-dependent. In addition, bevirimat demonstrates clinical activity in patients with HIV-1 strains resistant to other antiretrovirals. The pharmacokinetic profile of bevirimat allows once-daily dosing with limited potential for drug interactions. Bevirimat also has a tolerability and safety profile that appears to be suitable for long-term dosing. Further studies to evaluate the efficacy and tolerability of bevirimat are in progress.

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