Abstract eBook

CROI 2020

Conference on Retroviruses and Opportunistic Infections

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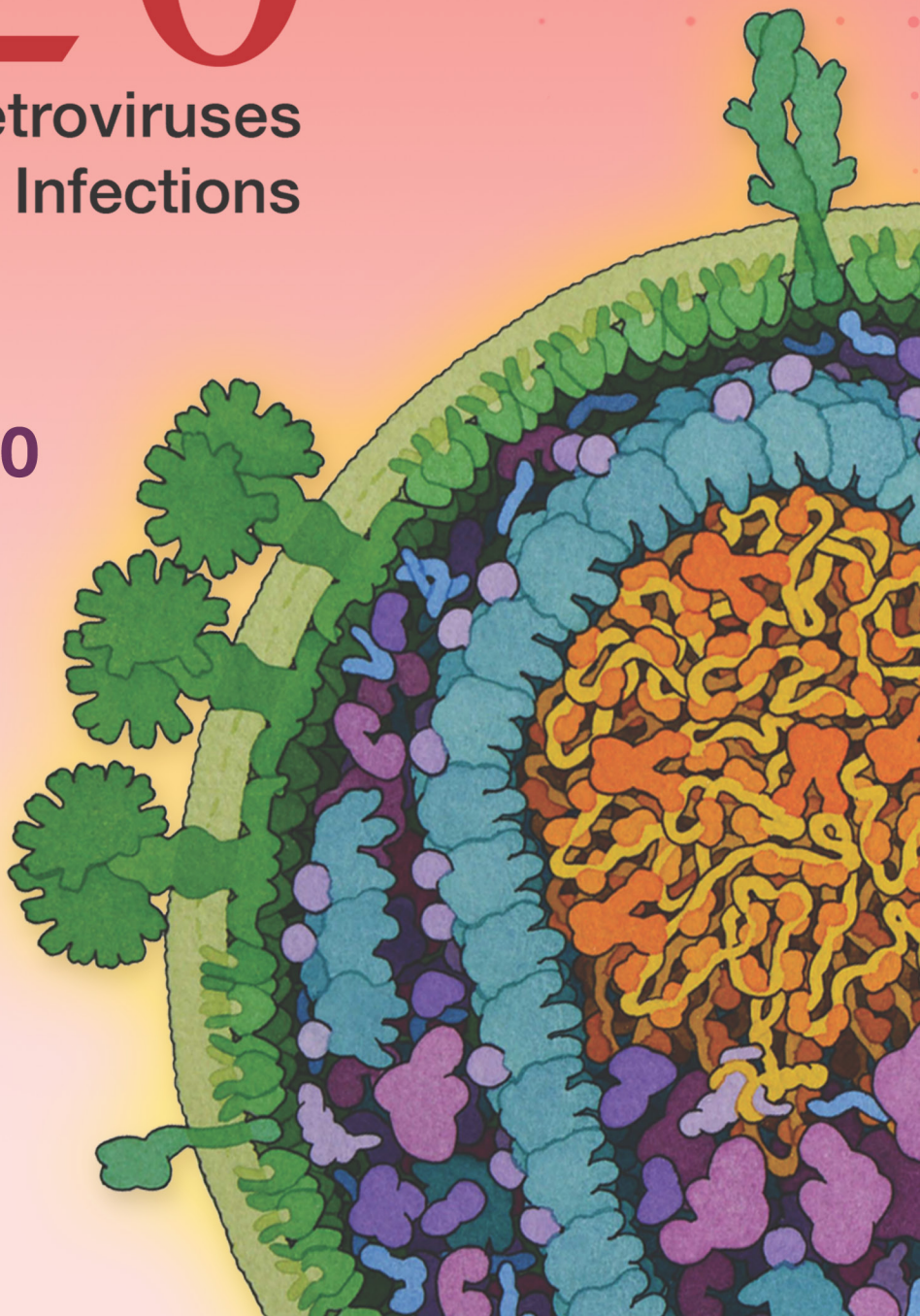

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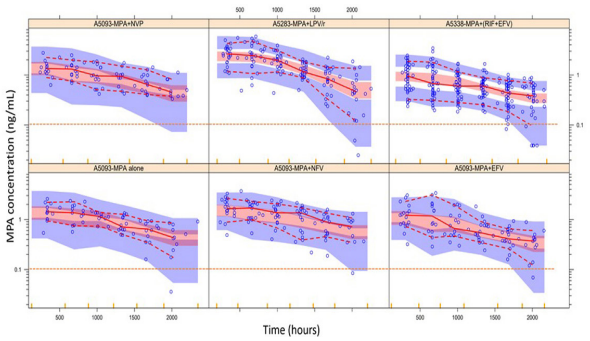
whereas LPV/r and NFV decreased clearance by 28.7% and 15.8%, respectively. LPV/r co-treatment was also found to accelerate the rate of slow release of MPA into systemic circulation, thus shortening the terminal half-life. The model predicted that, at week 12, a typical 60-kg woman on RIF+EFV and EFV has a higher risk of having a subtherapeutic concentration (3.4% and 2.6%) compared to MPA-alone (1.6%). This risk increased with body weight. Simulations demonstrated that re-dosing every 8-10 weeks can overcome the risk of contraceptive failure associated with these DDI.

Conclusion: Co-treatment with RIF+EFV, and to a lesser extent EFV alone, decreases systemic exposure of MPA, thus increasing the risk of subtherapeutic exposure and contraception failure. Dosing DMPA every 10 or even 8 weeks when prescribing RIF+EFV should eliminate this risk.

Visual predictive check of the final model (log scale) stratified by different study arms. The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observed data, while the shaded areas represent the 90% confidence intervals for the same percentiles, as predicted by the model. An appropriate model is expected to have all observed percentiles within the simulated confidence intervals



472 A LONG-ACTING NANOFORMULATED TENOFOVIR PRODRUG

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Background: Despite the success of existing antiretroviral therapy (ART) in controlling human immunodeficiency virus type 1 (HIV-1) infection, treatment requires life-long adherence to medicines. ART compliance can be compromised by frequency of dosing, and long acting formulations could potentially improve patient adherence. However, the hydrophilic nature of nucleoside reverse transcriptase inhibitors (NRTI) limits their transformation into long acting formulations. To this end, tenofovir (TFV), a NRTI, was modified into two different lipophilic prodrugs (M1TFV and M2TFV) to extend the apparent drug half-life, improve potency and facilitate access to viral replication sites.

Methods: TFV was modified and formulated into long acting lipid nanocrystals by high-pressure homogenization. The created TFV prodrugs were purified by silica column chromatography and characterized by NMR and FTIR. Nanoparticles were produced by high-pressure homogenization (NM1TFV, NM2TFV). Human monocyte derived macrophages (MDM) and CEM-ss T-cells were used as a biological platform to measure drug uptake and retention. Drug levels were quantitated in cell lysates by UPLC-TUV. After MDM treatment with 100 µM NM1TFV cells were challenged with HIV-ADA at a MOI of 0.1 at five day intervals for one month. Culture fluids were assayed for reverse transcriptase activity and cell-based HIV-p24 antigens recorded by immunohistochemistry. To assess the pharmacokinetic (PK) profile of these TFV prodrug formulations, male Sprague Dawley rats were injected with 75 mg/kg TFV equivalents of NM1TFV, NM2TFV, or TAF. Plasma, blood and peripheral blood mononuclear cells were collected weekly after injection. At the end of the four-week study, organs and tissues were collected for analysis of prodrug, parent drug, and triphosphate levels.

Results: Prodrug modifications enhanced drug uptake compared to tenofovir alefenimde fumarate (TAF) in both MDM and CEM-ss T-cells. M1TFV and M2TFV nanoparticles showed sustained prodrug levels in MDM for 30 and 15 days respectively; whereas TAF was eliminated within a day. In cellular efficacy studies, single treatment of ND1TFV restricted viral replication for 30 days. Analysis of the preliminary rat PK study is currently ongoing.

Conclusion: Long acting TFV formulations were developed and preliminary studies showed enhanced cellular uptake and sustained anti-HIV activity in vitro single dosing when compared against TAF. These results are promising for development of a long-acting TFV for HIV treatment and prevention.

473LB SAFETY AND PK STUDY OF VM-1500A-LAI, A NOVEL LONG-ACTING INJECTABLE THERAPY FOR HIV

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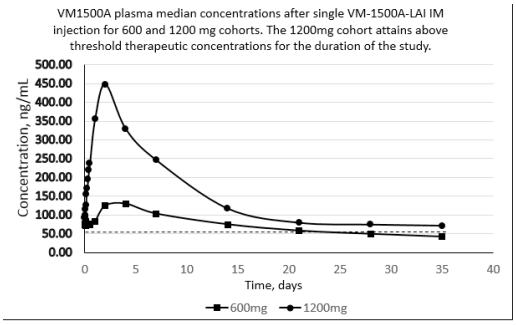
Background: VM1500A is a novel, potent NNRTI with unique clinical PK profile and broad-spectrum activity across HIV-1 variants. An oral dosage form of elsulfavirine, a pro-drug of VM1500A, has been approved in 2017 in Russia for treatment of HIV-infected patients in combination with standard antiretroviral therapy, under the brand name Elpida®. A long-acting injectable (LAI) form of VM1500A has been developed to expand the dosing options of VM1500A.

Methods: This Phase 1 trial is an ongoing open-label, single-center study to evaluate safety, tolerability and pharmacokinetics of single and multiple ascending intramuscular (IM) doses of the LAI nano-formulation of VM-1500A (VM1500A-LAI) in HIV-uninfected volunteers.

Results: 30 HIV-uninfected volunteers were enrolled and received single ascending doses (SAD) of VM-1500A of 150, 300, 600, and 1200 mg, after a 2-week dosing of 20 mg Elpida® capsules qd. The subjects were evaluated for 35 days post-injection and during that period provided serial blood samples for PK assessments. In the SAD cohorts, the main PK parameter was the sustained median plasma concentration of VM1500A above the target trough level (associated with efficacy of daily oral dose of 20 mg of Elpida® during 96 weeks treatment in HIV-infected patients) C_{trough} of 61 ng/ml. Upon completion of the 1200 mg, enrollment of subjects to receive multiple IM injections (once per month) was recommended by the SRC and is currently ongoing. In the SAD part of the study, a total of 21 male (5 Asians, 16 Caucasians) volunteers with a mean age of 26 y.o. and mean BMI of 23.9 kg/m_2 were enrolled. There were no significant baseline differences between the groups. The observed PK profile of IM VM-1500A-LAI is consistent with sustained delivery. Median (range) plasma concentrations of VM1500A at 35 days post-injection were 71 (52, 190), 42 (29, 44), 25 (17, 28) and 19 (12, 19) ng/ml for the 1200, 600, 300 and 150 mg dose levels, respectively. All doses were well tolerated and no-dose limiting toxicities were reported. Injection site related pain was notable at the highest dose tested. There have been no death or serious adverse event. Most AEs were mild (Grade 1) and resolved.

Conclusion: VM-1500A-LAI IM qm of 600 mg achieved median plasma C_{trough} above target trough level for at least 3 weeks. VM-1500A-LAI IM qm of 1200 mg achieved median plasma C_{trough} above target for 35 days and above. VM1500A LAI was tolerated and had an acceptable PK profile in healthy volunteers following single IM dosing in a range of 150mg to 1200mg.

VM1500A plasma median concentrations after single VM-1500A-LAI IM injection for 600 and 1200 mg cohorts. The 1200mg cohort attains above threshold therapeutic concentrations for the duration of the study.



474 CD4/CD8 RECOVERY AND FIRST-LINE ART: GREATEST IMPROVEMENT WITH INTEGRASE INHIBITORS

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