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Abstracts

Session 1

Pharmacokinetics / Resistance / Inhibitory Quotient

Abstract: 1

Pharmacokinetics/Resistance/Inhibitory Quotient

Predictive factors of Atazanavir response including genotypic inhibitory quotient in treatment-experienced patients

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Background: Atazanavir (ATV) is a novel and well-tolerated HIV protease inhibitor (PI). We evaluated the pharmacologic and virologic predictive factors of the response to ATV in pre-treated HIV-infected patients.

Materials & Methods: Patients receiving ATV as part of their antiretroviral regimen were prospectively evaluated. ATV Ctrough were determined by HPLC at steady-state. Parameters assessed were plasma HIV-RNA (VL), CD4-cell counts, drug-resistance mutations (ANRS v.12 algorithm), and the genotypic inhibitory quotient calculated as predicted Ctrough/number of PI resistance mutation (total-gIQ) and predicted Ctrough/number of ATV specific resistance mutation (ATV-gIQ). Virologic response was defined as VL < 400 copies/mL or VL decrease >1 Log. Statistical analysis was performed using SPSS/STATA.

Results: Data from 36 and 14 patients followed-up for 12 and 24 weeks, respectively, were analyzed: median age, 40 years; male, 72%; median number of previous antiretroviral regimen, 8 (range: 0-20); number of previous PI, 2 (0-5). ATV was given with RTV at the 300/100 mg QD dose in 32/36 patients. Median baseline (BL) VL and CD4 count were 4.3 Log and 178 cells/μL, respectively. At BL, median (range) number of PI and ATV specific mutations were 3 (0-15) and 1 (0-10), respectively. Median (range) ATV Ctrough, total-gIQ and ATV-gIQ were 705 ng/ml (50-1504), 184 (10-773) and 391 (50-843), respectively. At W12, 29/36 patients with BL VL >400cp/ml had a median VL drop of -1.65 Log and 26/36 (72%) were virologic responders with a median CD4 gain of 69 cells/μL. At W24, 9/14 (64%) still had undetectable VL (median CD4 gain 48 cells/μL). Virologic responders at W12 had higher median ATV-gIQ (459 vs. 126; p=0.07) and CD4 gain (+69 vs. +3 cells/μL; p=0.014) and lower median number of PI mutations (3 vs. 7.5; p=0.001) and ATV specific mutations (1 vs. 5; p<0.001) at BL compared to non responders. In the multivariate analysis, only ATV-gIQ, number of PI mutations at BL and nadir of CD4 were significantly associated with a higher VL drop at W12 (p=0.029, p=0.015 and p=0.022).

Conclusions: In treatment experienced-patients, ATV-gIQ could be a better predictive factor of early virologic response than the number of ATV resistance mutations at BL or total-gIQ.

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Pharmacokinetics/Resistance/Inhibitory Quotient

Pharmacokinetic/Pharmacodynamic-Disease modelling and simulation in the development of Maraviroc (UK-427,857)

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Background: Maraviroc (UK-427,857, MVC) is a CCR5 inhibitor currently in full development for the treatment of HIV infection. Modelling and simulation were performed to describe and predict dose response relationships to facilitate the development programme for MVC.

Materials & Methods: An integrated Pharmacokinetic(PK)-Pharmacodynamic(PD)-disease model was developed which incorporated the following submodels: adherence..PK..PD..virus and cell dynamics (disease model). The initial disease model was adapted from a published model for other classes of antiretrovirals. Nonlinear-mixed effect modelling with NONMEM® (Globomax) was used for parameter estimation while Trial Simulator® (Pharsight) was used for the simulation of trial outcomes.

Results: The model (parameters and submodel components) was updated in a stepwise fashion as clinical data became available and increased complexity was required: Step1: A model was developed prior to the availability of clinical data for MVC, utilising in vitro IC50 data for MVC, literature and in-house viral dynamic data. Simulations were performed to inform the design of a proof of principle monotherapy study. Step 2: The model parameters were updated with PK and viral load data from the first monotherapy study. The updated model was used for simulation to design a second monotherapy study to assess dose regimen (QD versus BID) and food effects. Step 3: Data from both monotherapy studies were used to re-estimate model parameters. An updated and extended simulation model which accounted for combination therapy (literature), adherence (literature), and resistance was utilised for predictions of long term treatment response in antiretroviral naïve and experienced patients.

Conclusions: This model based approach has influenced trial design and dose selection in Phase 2a and Phase2b/3.

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Pharmacokinetics/Resistance/Inhibitory Quotient

Once-Daily Versus Twice-Daily Regimens: Which is Best for HIV Infected Patients?

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Background: Today most protease inhibitors (PIs) are dosed twice-daily (BID), although the increased apparent half-life of PIs in the presence of ritonavir makes possible its combined use in making once-daily (QD) dosing. Here we analyze which regimen provides superior internal PI exposure when actual dosing patterns are taken into account.

Materials & Methods: We have systematically identified all the HIV-infected patients in the newly-compiled AARDEX Pharmionics database that were prescribed a PI and had their dosing histories electronically compiled: 237 patients with a QD regimen, 245 with a BID regimen.

Results: The proportion of patients with the prescribed number of doses taken is higher ($p < 0.0001$) with QD (93.5%) than with BID (84.5%) dosing. During BID dosing, the evening dose is much more frequently omitted than the morning dose. Moreover, the pharmacokinetic consequences of missing a single QD dose are similar to those of missing two consecutive BID doses. The probability of two consecutive dose omissions in the BID regimens was less than half the probability of missing a single QD dose.

Conclusions: The long-standing promotion of QD regimens as having 'superior compliance' is based on the modest superiority of percentage of prescribed doses taken with QD vs BID regimens. The factor critical for superior therapeutics, however, is internal exposure, and there the projected impact on PI concentrations of actual dosing histories in almost 500 patients indicates substantial superiority of the BID regimen.

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Pharmacokinetics/Resistance/Inhibitory Quotient

Pharmacological and cross-resistance profiling of PL-100 and its pro-drug, PPL-100

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Background: We reported previously that PL-100 has a favorable cross-resistance profile against 14 resistant HIV isolates. However, some pharmacological parameters of this novel protease inhibitor (PI) are not optimal. In the current study, a phosphorylated pro-drug (PPL-100) has been developed to improve solubility and pharmacokinetics of the parent compound (PL-100). We have also further characterized the cross-resistance profile of PL-100 against 49 additional HIV isolates with reduced susceptibility to all approved PIs including atazanavir.

Materials & Methods: PL-100 and PPL-100 were evaluated for pharmacokinetic profiling in vivo. Solubility was determined using a standard LC-MS method. Antiviral activity of PL-100 was determined against 49 diverse multi-PI resistant strains using PhenoSense assay (ViroLogic Inc). For comparison, atazanavir, saquinavir, indinavir, nelfinavir, amprenavir, and lopinavir were tested in parallel.

Results: PPL-100 was found to be >1000-fold more water soluble than PL-100 and had shown 2- to 3-fold improvement over PL-100 in key pharmacokinetic parameters such as C_{max} and oral bioavailability. This pro-drug had low systemic exposure and was metabolically converted to PL-100. The bioavailability of PPL-100 can be further boosted by ritonavir. In cross-resistance profiling studies against 63 PI-resistant viruses, PL-100 had a median EC₅₀ fold-change (FC) of 3.6. The median EC₅₀ FC of 6 approved PIs above ranged from 8.1 (indinavir) to 23 (saquinavir). Furthermore, 37% of resistant strains had FC <2.5 to PL-100 and 76% of them showed FC < 10. In comparison, the % strains with FC < 2.5 to 6 approved PIs ranged from 9.5 (lopinavir) to 27% (saquinavir). The % strains with FC < 10 to these approved drugs ranged from 27 (nelfinavir) to 54% (indinavir).

Conclusions: PPL-100 has shown substantially improved solubility and pharmacokinetics. Taken together with the favorable cross-resistance profile displayed by PL-100, PPL-100 has potential as a novel PI for treatment of patients infected with PI-resistant HIV strains.

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Pharmacokinetics/Resistance/Inhibitory Quotient

Fosamprenavir (FPV) trough concentrations (C_{min}) and inhibitory quotients (IQ), at steady-state, in plasma and lymphocytes of HIV Infected patients receiving different dosage regimens

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Background: Inhibitory quotient seems to be one of the most promising predictive surrogate markers of protease inhibitors PIs efficacy. It has been shown that the intracellular penetration of PIs could be different depending on the dosage regimen. We determined in vivo APV IQs, in plasma and lymphocytes, following three different FPV/r_{tv} dosage regimens.

Materials & Methods: 10 HIV infected pts, treated with Agenerase/r 600/ 100 mg received boosted fosamprenavir (FPV) in a cross over study as follows: 700/100 mg bid, 1400/100 mg and 1400/200 mg QD. Serial blood samples were obtained once steady-state was reached for each treatment. Mononuclear cells were separated from blood at C_{min} and C_{max} samples to specifically determined intracellular APV level. Pharmacokinetic parameters in plasma were estimated by using a non compartmental analysis model. The IC₅₀ used to estimate IQs were 14.6 ng/mL (wild type) (WT) and 61.4 ng/mL (mutated strains)(MT).

Results: The median plasma area under the curve, calculated at 24 h (AUC₂₄) was slightly higher for 700/100 bid and 1400/200 QD (54.8 and 50 mg.h.L⁻¹) by comparison with 600/100 bid and 1400/100 (40.6 and 44.9 mg.h.L⁻¹). Median C_{min} in plasma/cells were: 1.34/3.95, 1.78/4.5, 1.08/4.6 and 1.28/3.55 mg/L for 600/100, 700/100, 1400/100 and 1400/200 respectively. Plasma IQs were much higher with both bid dosage regimens for either WT and MT, i.e, 103 and 137 for 600/100 and 700/100 respectively (WT) and 25.6 and 32.5 for MT; while the QD dosage regimen provide lower IQs, with 69.2 and 80.8 (1400/100 and 1400/200) (WT) versus 16.45 and 19.2 (MT) . In cells, all the dosage regimens provided very high IQs for both WT and MT. Indeed for WT the IQs were 270 (600/100), 308 (700/100), 315 (1400/100) and 243 (1400/200) while for MT the values were lower but still elevated values with 64.3, 73.2, 75 and 57.8.

Conclusions: In HIV infected patients treated with boosted FPV, APV reached higher intracellular concentrations than in plasma. This results in very high IQs particularly inside the cells whatever the dosage regimen including both WT and MT HIV strains.

Abstract: 6 Pharmacokinetics/Resistance/Inhibitory Quotient

Pharmacokinetic parameters of Efavirenz in patients receiving an intermittent EFV-based antiretroviral treatment : a Substudy of the ANRS 106 Window Trial

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Background : The ANRS 106 WINDOW trial is an open randomized 96-week (w) trial comparing intermittent therapy (IT: 8 w on / 8 w off) to continuous therapy (CT) among 400 patients with chronic HIV-1 infection, stable HAART, HIV-1 RNA (VL) < 400 cp/ml and CD4 > 450/mm³ for at least 6 months ; primary endpoint is immunologic. When the patients receiving an efavirenz (EFV)-based IT regimen came off therapy, they stopped EFV straightaway and the other drugs 7 days later.

Materials & Methods : Pharmacokinetic study was planned in a subgroup of patients receiving an EFV-based IT regimen. The objective was to evaluate the pharmacokinetics of EFV plasma concentrations during the interruption phase. Blood samples were drawn on day 1, 12h after last EFV dosing, then on days 3, 7 and 10. EFV concentrations were measured by a validated HPLC assay. The lower limit of quantification (LLQ) was 50 ng/ml. PK was repeated at a next interruption phase in 9 pts with EFV concentrations < 312 at day 3 or > 625 ng/ml at day 7. EFV half-life was calculated from the concentrations versus time mono-exponential decline.

Results: 21 patients (15 males) were evaluated (mean 39 years). EFV-associated ARV drugs included NRTI in all patients plus a protease inhibitor in 3 patients. Median [range] EFV concentrations (ng/ml) on days 1, 3, 7 and 10 were : 1962 [728-4146], 416 [95-1390], 112 [<50-749] and 50 [<50-631] respectively. EFV half-lives ranged from 27h up to 136h (median : 47h, coefficient of variation 54%). In contrast, intra-subject variability was low in the 6 patients who experienced a second complete PK evaluation. After 8 weeks of HAART resumption following the considered interruption phase, VL decreased to < 400 cp/ml in 19/21 patients.

Conclusions: EFV half-life was highly variable among patients without influence on the short-term viral response after treatment resumption. Data suggest that closer and individualized drug monitoring of patients undergoing EFV treatment interruptions should be recommended. Virologic impact, including resistance remains to be deeply investigated.

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Pharmacokinetics/Resistance/Inhibitory Quotient

Intracellular inhibitory quotients (IQs) for Abacavir and Tenofovir – Abacavir has a higher IQ

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Background: The IQ is a theoretical method to integrate drug exposure and viral susceptibility as predictors of clinical outcome. IQs have clinical utility in predicting treatment response for protease inhibitors (PI); the larger the IQ the greater the efficacy and demonstrate that plasma drug concentrations only partially explain clinical outcomes. The nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are anabolized to their active phosphorylated moieties at the intracellular level; it is therefore more difficult to determine active drug concentrations and hence IQs for this class of drugs. This study was conducted to evaluate the intracellular IQs (IIQs) for two widely prescribed NRTIs, abacavir and tenofovir disoproxil fumarate, both administered once daily (QD).

Materials & Methods: IIQs were modeled using the ratio of published trough intracellular active phosphorylated moiety concentrations to viral susceptibility (IC₅₀), as well as to measures of reverse transcriptase inhibition (K_i; K_i = inhibitory constant for inhibition by competitor of incorporation of endogenous triphosphate into DNA by HIV-1 reverse transcriptase enzyme). Intracellular (peripheral blood mononuclear cell; PBMC) trough concentrations for the active moieties of abacavir (carbovir triphosphate; CBV-TP) and tenofovir (tenofovir diphosphate; TFV-DP) and IC₅₀ and K_i values were the most conservative obtained from the published literature.

Results: IIQs determined with the predicted intracellular concentration needed to inhibit reverse transcriptase (K_i) for CBV-TP and TDF-DF at the 24 hour time point were 4 and 2, respectively. Similarly, when virus susceptibility was measured using in vitro IC₅₀ values the IIQs were 2 and 0.1 for CBV-TP and TDF-DF, respectively. The plasma concentrations of tenofovir and abacavir do not correlate with the IIQs for these two drugs.

Conclusions: Abacavir administered QD has a calculated IIQ 2 fold greater than tenofovir, suggesting that despite a shorter intracellular half-life, ABC retains higher antiviral activity