The Effects of Aging on the Pharmacokinetics of Nelfinavir and M8 in HIV-1-infected individuals

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BACKGROUND

- In the elderly, clearance of omeprazole (a CYP2C19 substrate) is significantly decreased suggesting reduced CYP2C19 activity with aging;
- Nelfinavir (NLF) is primarily metabolized by CYP2C19 to its active metabolite M8. M8 is then metabolized by CYP3A4;
- We hypothesize that aging may increase and decrease NLF and M8 exposure, respectively, and cause a decrease in the M8/NLF metabolic ratio.

STUDY OBJECTIVE

- To investigate the effects of aging on the steady-state pharmacokinetics (PK) of nelfinavir, M8 and the metabolic ratio in HIV-1-infected individuals.

METHODS

- Steady-state 12 hour intensive PK study

Inclusion criteria

- Patients on nelfinavir 1250 mg BID (625 mg tablet formulation) and 2 NRTIs for more than 2 weeks
- Signed written informed consent
- ≥ 18 years of age
- Stable medical condition

Exclusion criteria

- Concomitant medications known or thought to interact with nelfinavir or M8 (2C19/3A4 inhibitors or inducers, acid-modifying agents)
- Acute illness
- Pregnant, breastfeeding or at risk of becoming pregnant during study
- Suspected non adherence

Pharmacokinetic sampling and analysis

- Standardized breakfast (617 kcal, 18g fat)
- PK sampling pre-dose and at 1, 2, 3, 4, 5, 6, 8 and 12 hours post-dose
- Analytical method: validated LC/MS/MS assay (Ottawa, Canada)
- PK parameters calculated using non compartmental methods
- Molecular weight adjusted $AUC_{0-\tau}$ M8/ $AUC_{0-\tau}$ NLF metabolic ratio

STATISTICAL ANALYSIS

- Sample size needed: 24 patients, 6 patients per age group (≤ 39, 40-49, 50-59, ≥ 60 years)
- Linear regression between age and each PK parameter and metabolic ratio
- Ln-transformed PK parameters compared using T-tests for patients < 50 years and ≥ 50 years of age
- S-Plus® 8.0 for Windows

RESULTS

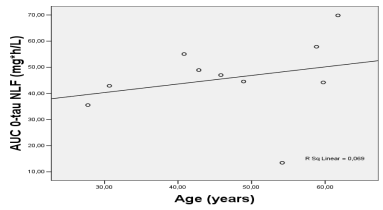
PATIENT DEMOGRAPHICS BY AGE GROUP (n=10)

Age group	≤ 39 (n=2)	40-49 (n=4)	50-59 (n=3)	≥ 60 (n=1)	< 50 (n=6)	≥ 50 (n=4)
Mean age ± SD	29.2 ± 2.1	45.8 ± 3.5	57.6 ± 3.0	61.8	39.5 ± 8.5	58.6 ± 3.2
Mean weight (kg) ± SD	73.5 ± 7.9	70.3 ± 17.5	66.0 ± 10.3	64.0	71.4 ± 14.1	65.5 ± 8.4
Mean BMI (kg/m²) ± SD	25.6 ± 2.1	24.5 ± 3.5	22.4 ± 3.1	22.7	24.8 ± 2.9	22.5 ± 2.6
% male	0	75	100	100	50	100
Race (%)						
- Black	100	0	0	0	33.3	0
- Caucasian	0	75	100	100	50	100
- Other	0	25	0	0	16.7	0

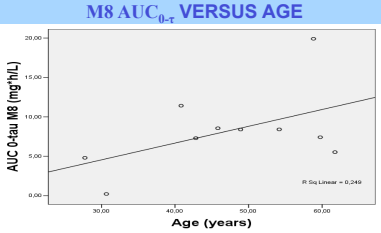
PK PARAMETERS NELFINAVIR (geometric mean)

	$AUC_{0-\tau}$ mg*h/L	Cmax mg/L	Cmin mg/L	CL/F L/h
≤ 39 (n=2)	39.04	5.68	1.06	32.02
40-49 (n=4)	48.73	6.65	1.57	25.65
50-59 (n=3)	32.53	4.87	0.95	38.43
≥ 60 (n=1)	69.83	10.10	3.85	17.90
< 50 (n=6)	45.26	6.31	1.38	27.62
≥ 50 (n=4)	39.37	5.84	1.35	31.75
	$AUC_{0-\tau}$ mg*h/L	Cmax mg/L	Cmin mg/L	M8/NLF
≤ 39 (n=2)	1.01	0.15	0.03	0.025
40-49 (n=4)	8.79	1.24	0.25	0.172
50-59 (n=3)	10.74	1.88	0.22	0.315
≥ 60 (n=1)	5.52	0.97	0.26	0.075
< 50 (n=6)	4.27	0.62	0.12	0.090
≥ 50 (n=4)	9.10	1.60	0.23	0.220

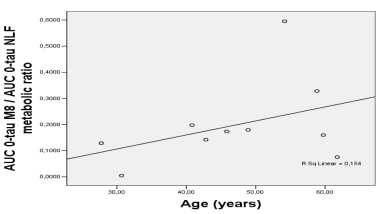
NELFINAVIR $AUC_{0-\tau}$ VERSUS AGE



M8 $AUC_{0-\tau}$ VERSUS AGE

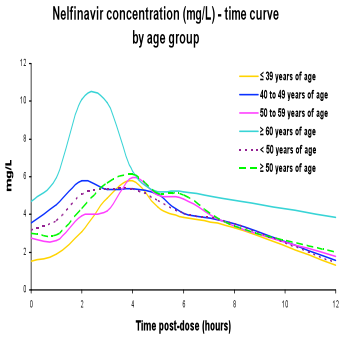


$AUC_{0-\tau}$ M8 / $AUC_{0-\tau}$ NLF METABOLIC RATIO VERSUS AGE



- 10/24 patients so far have completed the study
  - 3 female, 7 male
  - 70% Caucasian
  - mean age 47.1 ± 11.9 years
  - mean CD4⁺ 447 cells/mm³
  - 80 % undetectable viral load
- Unexpected contamination of NLF tablets with ethyl methane sulfonate (EMS) reduced NLF use and curtailed patient enrolment

MEDIAN NELFINAVIR CONCENTRATIONS



- The PK parameters and metabolic ratio were not statistically associated with age;
- If we remove the outlier in the 50 to 59 year age group, the $AUC_{0-\tau}$ (p=0.046) and CL/F (p=0.036) are associated with age;
- The geometric means of the PK parameters for the < 50 versus the ≥ 50 age groups were not significantly different.

DISCUSSION / CONCLUSIONS

- Small sample size limits the results;
- Trend towards increased $AUC_{0-\tau}$ and decreased CL/F with aging, but not statistically significant;
- High interpatient variability that may be explained in part by pharmacogenetics;
- The present results do not support the hypothesis of decreased CYP2C19 activity with aging and subsequent increased NLF concentrations, decreased M8 concentrations and decreased M8/NLF metabolic ratio;
- Recruitment is ongoing to validate these results.

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