IN SILICO PHARMACOKINETICS EVALUATION OF FORGIVENESS FOR DORAVIRINE & RILPIVIRINE

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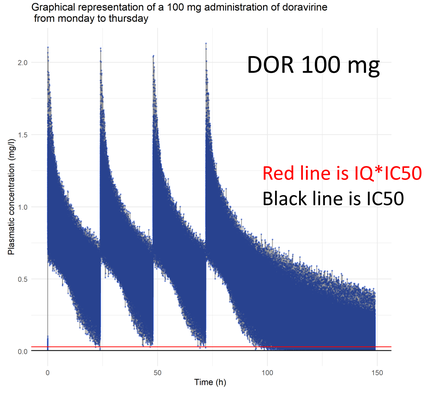
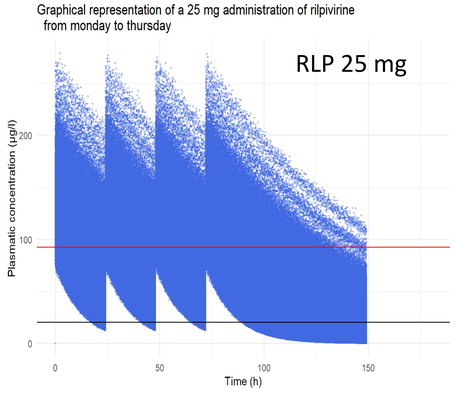
BACKGROUND

- ANRS 170 QUATUOR findings showed the non-inferiority of some intermittent maintenance treatment strategies, but treatment failures related to emerging disease-resistant mutations with rilpivirine (RLP) as third therapeutic agent have been observed.
- The aim of this study was to evaluate *in silico*, using simulation from population pharmacokinetics models, the concentrations of RLP and doravirine (DOR) after 3 days off, as the consequences of this strategy on non-nucleoside reverse transcriptase inhibitors (NNTI) concentrations are not known

METHODS

- Previously published population pharmacokinetic models for DOR (1) and for RLP (2) were implemented in the mrgsolve R package.
- 500 series of 10000 Monte Carlo simulations at steady state for 25 mg/day for RLP and 100mg/day for DOR were drawn without drug cessation and after 3 days off.
- The mean±SD proportion of simulated patient with C24h and C72h after 3 day off (C72h/3do) > IC50 (5.2 µg/L (DOR) ; 20.5 µg/L (RLP)) and IQ (6 * IC50 (DOR); 4.5 * IC50 (RLP)) were calculated for both drugs.
- Nomograms to estimate the probability of having a concentration > IC50 or IQ after 72h of drug cessation for different range of C24h were built.





1) We found that treating with Doravirine is more forgiving than with Rilpivirine as shown by the larger proportion of patients with effective drug exposure after 3 days off.

2) The trough concentration could be a reliable marker to predict the forgiveness

RESULTS

- Simulated C24h median [range] for RLP were 60.4 [17-179] µg/L and for DOR 397 [170-646] µg/L.
- The proportion of patient with C24h>IC50, C72h/3do >IC50 and C72h/3do >IQ were 100%, 16±0.4% and 0% for RLP and 100%, 89±0.4% and 40.2±0.5% for DOR.
- The nomogram for probability of target attainment at 72h as function of C24 range is presented below.

Table 1 Probability of effective concentration after 72h of forgiveness from Ctrough at 24h.

Doravirine 100 mg OD			Rilpivirine 25 mg OD		
C24 interval (µg/L)	Probability C>IC50 at 72h (%)	Probability C>IC50*IQ at 72h (%)	C24 interval (µg/L)	Probability C>IC50 at 72h (%)	Probability C>IC50*IQ at 72h (%)
170±3.1 -273±1.8	27.2±1.6	0±0	16.6±0.4 -30.5±0.3	0.1±0.1	0±0
273±1.8 -315±1.4	63.4±1.9	0.1±0.1	30.5±0.3 -38.9 ±0.3	0.3±0.2	0±0
315±1.4-345±1.3	86±1.2	1.4±0.4	38.9±0.3 -46.1±0.3	0.7±0.3	0±0
345±1.3-372±1.3	95.4±0.7	7.6±1.0	46.1±0.3 -53.1±0.3	1.4±0.4	0±0
372±1.3 -397±1.2	98.7±0.4	21.1±1.5	53.1±0.3-60.4±0.3	2.8±0.5	0±0
397±1.2 -421±1.3	99.7±0.2	41.1±1.9	60.4±0.3-68.5±0.4	5.6±0.8	0±0
421±1.3-449±1.4	99.9±0.1	63.2±1.8	68.5±0.4 -78.1±0.5	11.1±1	0±0
449±1.4 -481±1.5	100±0	82.2±1.5	78.1±0.5 -90.6±0.6	21.9±1.5	0±0
481±1.5-525±1.8	100±0	94.3±0.8	90.6±0.6 -110.1±0.8	43.0±1.8	0±0.1
525±1.8 -646±4.4	100±0	99.3±0.2	110.1±0.8 -178.8±2.8	79.6±1.6	0.7±0.3

CONCLUSIONS

- Based on these findings, treating with DOR would be more forgiving than with RLP since DOR exhibits a larger proportion of patients with effective drug exposure.
- The main limit of this work is that we only evaluated the drug concentrations that cannot be a perfect surrogate of the drug effect.
- However, DOR is a promising third therapeutic agent suitable for an intermittent maintenance treatment strategy.
- Further studies are needed to confirm this assumption and evaluate the developed nomograms.
- **Limitations**
  - Simulations drawn for a single molecule: not the real life situation.
  - Strong hypothesis: plasmatic concentrations reflects the pharmacodynamics effect.

ADDITIONAL KEY INFORMATION

(1) Yee et al, Antimicrob Agents Chemother. 2019
(2) Aouri et al, Antimicrob Agents Chemother. 2016

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