Pharmacokinetics of Levofloxacin in M(X)-DR tuberculosis patients.

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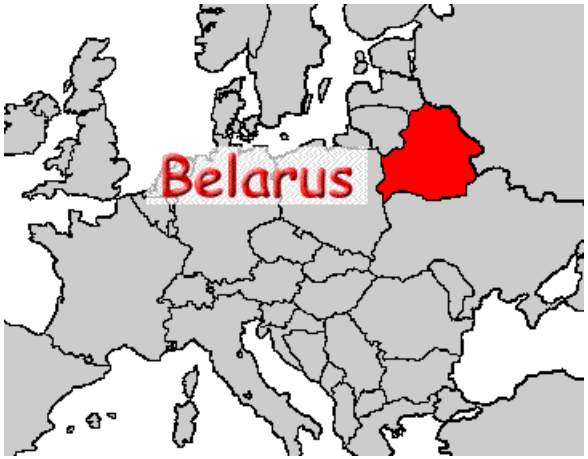


- 5.000 TB patients diagnosed each year
- 3.000 bacteriological confirmed diagnosis.
- Survey nov.'09- dec.'10, Minsk, population of 1.8 mln:
  - New treated TB - 35.3% MDR-TB and 2.0% XDR-TB.
  - Previously treated TB -76.5% MDR-TB and 19.4% XDR-TB[8].
- OFX resistance:
  - 14.5% (new MDR-TB).
  - 46.2% (previously treated MDR-TB).

[8] Skrahina et al. ERJ 2012

Why LFX

- Later-generation of FQs and WHO group 3 drug
- Affordable drug, comparing with MFX or GFX.
- Available drug in local market.
- Equivalent efficacy with MXF for treating MDR-TB (similar treatment success rate, sputum conversion, rate of adverse reactions) [6,7].

[6]Koh AJRCCM 2013, [7]Giang IJAA 2013

Activity of LFX

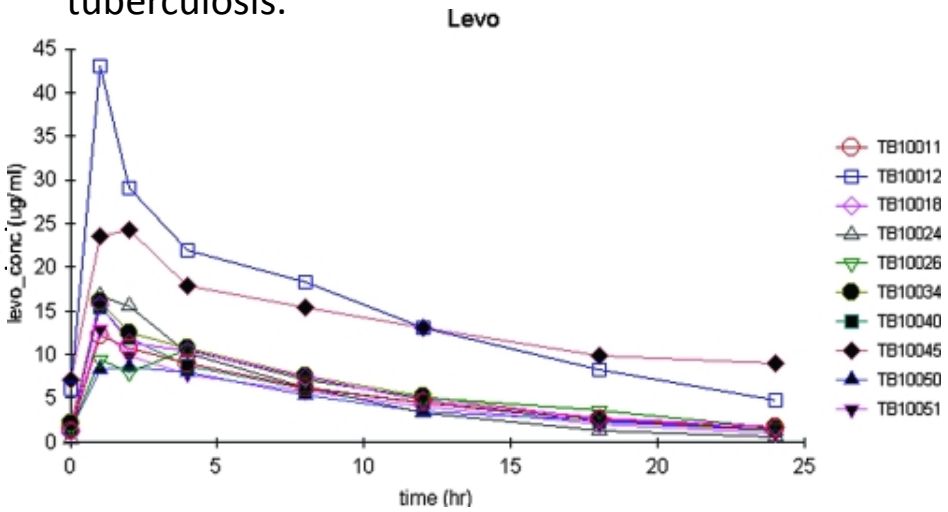
- High *in vitro* en *in vivo* bactericidal activity [1,2]
- Efficacy has been shown to be predicted by the AUC/MIC ratio [3]

[1], Ji et al, AAC 1995, [2] Rodrıguez et al IJAA 2002, [3]Peloquin et al, AAC 2008.

PK of LFX:

- >95% oral absorption.
- Good penetration into lung tissue, cerebro-spinal fluid and bone [4,5]
- 24% to 38% is bound to plasma proteins, independent of serum drug concentration.

Plasma concentrations of levofloxacin versus time after dosing in 10 adults with pulmonary tuberculosis.*



[4]Bano et al. JBMU 2011, [5] Thwaites et al AMC 2011, * Peloquin et al, AAC 2008

Objective

- To determine PK LFX M(X)DR-TB patients.
- To determine MIC values in M(X)DR-TB patients.
- To assess pharmacokinetic variability and potential consequence for AUC/MIC ratio.

Materials and Methods

- Pulmonary M(X)DR-TB
- Dose 15 mg/kg per os daily, rounded to 750-1000 mg.
- Samples taken at T= 0, 1, 2, 3, 4, 7, 12 hr at steady state.
- Sample analysis using LC/MS-MS analysis.
- Resistance:
  - Breakpoint testing using BACTEC MGIT960, 2 mg/L.
  - MIC testing 0.25-2.0 mg/L (7H10 and BACTEC MGIT960).
- Non-compartmental analysis (MW/Pharm®, version 3.82)
- Clinical data.

Results

Patients characteristics at baseline (n=20)

Female	8 (40)
Age yrs	31 (27-35)
Weight kg	63.4 (55.3-77)
Length cm	174 (167-182)
LBM	22.87 (11.1-37.2)
BMI kg·m^{-2}	20.1 (18.9-23.4)
Diagnosis: New Previous treated	 12 (60) 8 (40)

Data are presented as n (%) or median (interquartile range)

Pulmonary tuberculosis: Cavitary Non-cavitary	 13 (65) 7 (35)
Sputum: Smear-positive Culture-positive	 10 (50) 20 (100)
Resistance pattern: MDR XDR	 15 (75) 5 (25)
Comorbidity: Alcohol abuse Smoking Renal insufficiency HIV	 2 (10) 11 (55) none none

Results

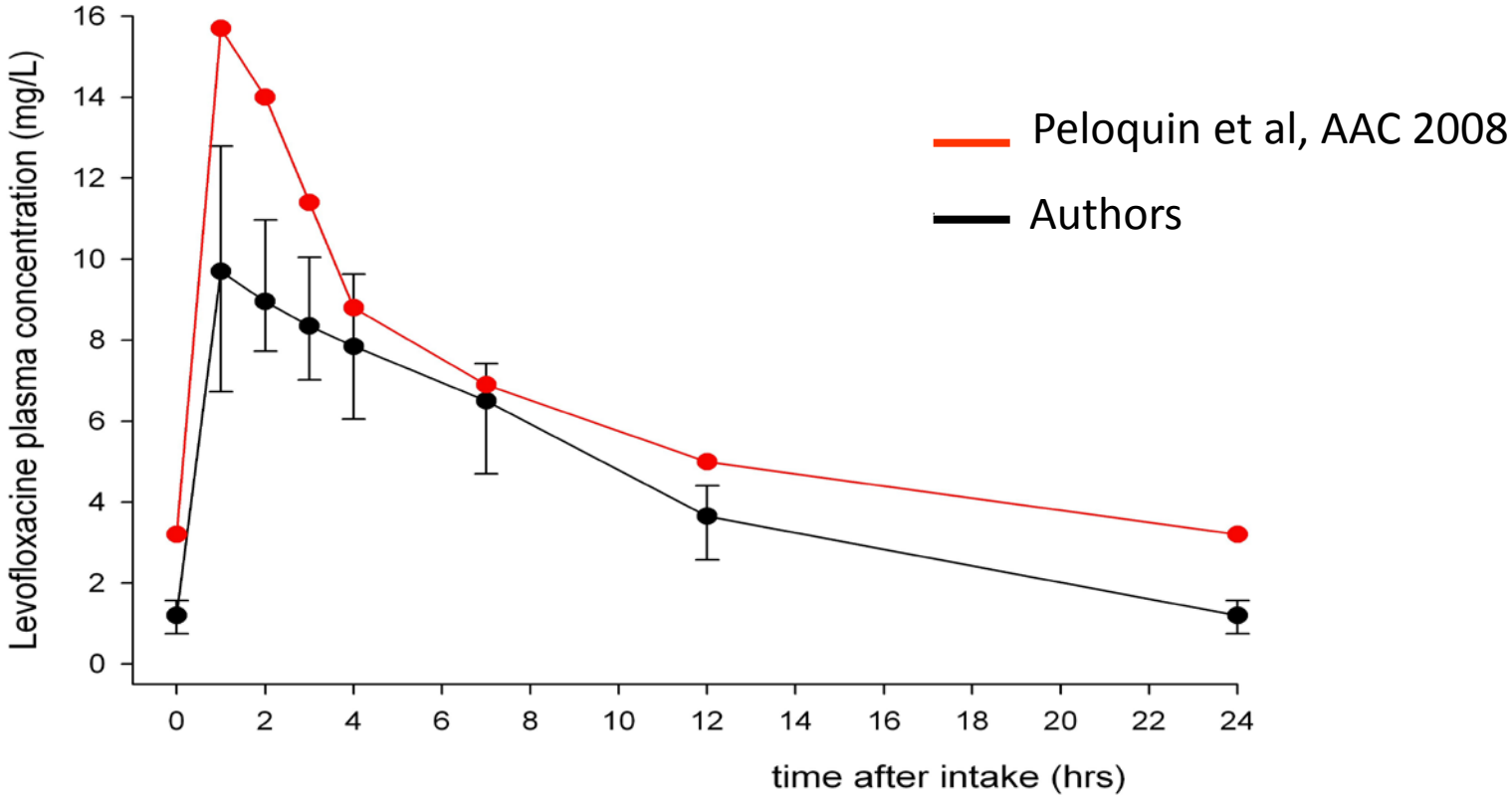
Steady-state pharmacokinetics of LFX.

Parameter	Levofloxacin (n=20)
AUC0–24h (mg*h/liter)	98.8 (84.8 – 159.6)
Cmax (mg/liter)	10.1 (8.4 – 16.2)
Cmin (mg/liter)	1,2 (0.9 – 4)
Tmax (h)	1 (1-7)
t1/2 (h)	6.7 (6 -16.3)
CL (liter/h)	8.3 (6.7 – 31.2)
V_d (liters)	88.2 (69.6 – 196.5)

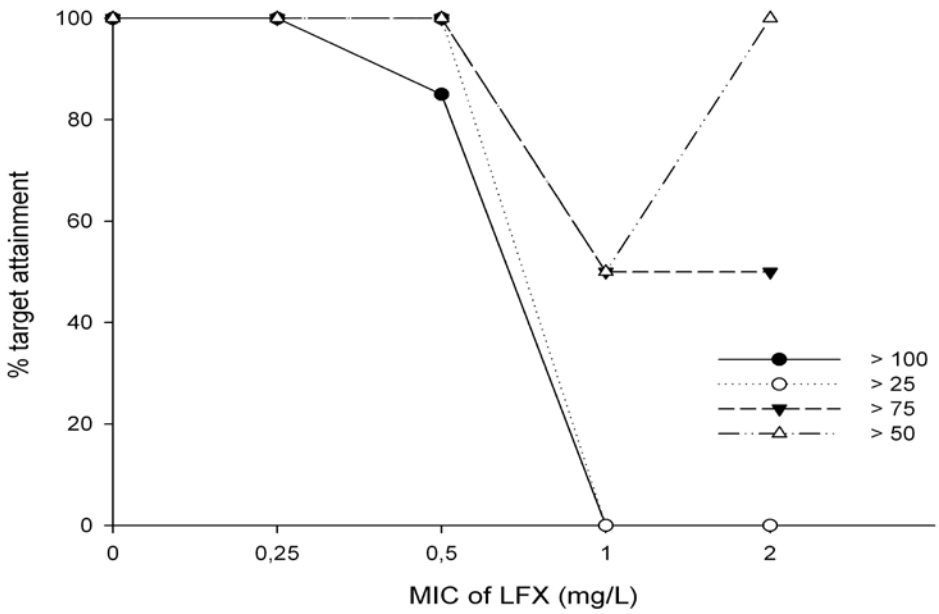
Data are presented in median values (IQR)

Results

Plasma concentration time curve of LFX.



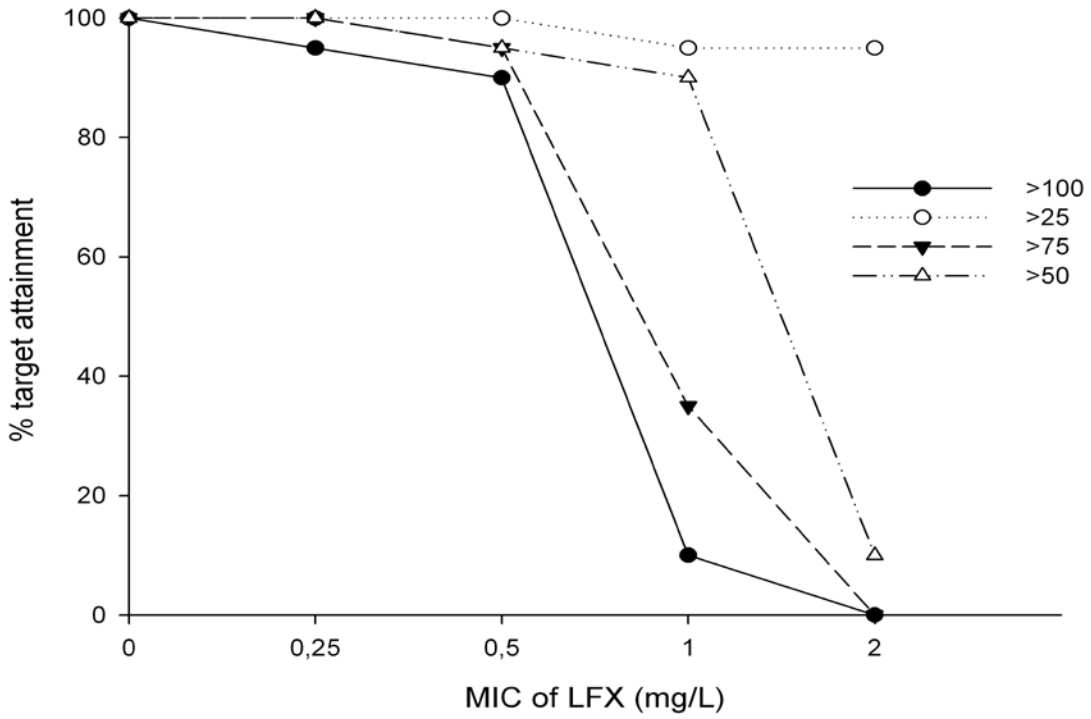
Target attainment (%) for MIC values based on individual PK-PD results (n=17)



MIC	AUC	fAUC/MIC
0,25	139,60	362,96
0,25	153,60	399,36
0,25	114,40	297,44
0,25	82,66	214,92
0,25	111,30	289,38
0,25	97,81	254,31
0,5	159,60	207,48
0,5	119,10	154,83
0,5	85,38	110,99
0,5	79,77	103,70
0,5	90,85	118,11
0,5	83,16	108,11
0,5	68,76	89,39
1	99,82	64,88
1	31,35	20,38
2	126,50	41,11
2	156,90	50,99

MIC 0.5 mg/L (IQR 0,25-2,0 mg/L).
*f*AUC0-24/MIC 109,5(IQR 89,39-399,36)

Target attainment (%) for varying MIC values based on individual PK results.



Discussion

- Identification of new susceptibility breakpoints.
- Dose exceeding 15mg/kg.
- PK variability of LFX is less then MFX

Conclusion

- Large variability in AUC, Cmax and MIC
- Targets *f*AUC0-24/MIC of ≥ 100 were only observed in case MIC values 0.25-0.5 mg/L.
- Prospective evaluation high-dose LFX is needed.