The impact of pyrazinamide resistance on the treatment outcome of patients with multidrug-resistant tuberculosis in Karakalpakstan, Uzbekistan

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Background

Pyrazinamide (PZA), is regarded as an important agent in the management of multi-drug resistant tuberculosis (MDR-TB) (defined as resistance to at least rifampicin and isoniazid) and has been shown to reduce treatment duration for drug-sensitive TB (1). Since the inclusion of PZA in a MDR-TB regimen adds significantly to both the pill burden and the side effects, (mainly arthralgia and hepatitis), it is logical to limit usage to patients where PZA has a proven effect.

The current World Health Organisation (WHO) recommendation is to include PZA in MDR-TB regimens unless there is demonstrated evidence of resistance (2). However, large-scale data supporting this recommendation are lacking.

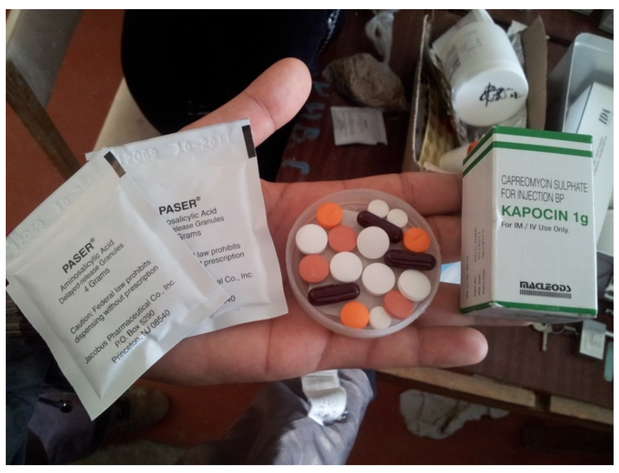
Aim

To assess the effect of PZA resistance upon treatment outcome amongst MDR-TB patients treated with a full intensive phase PZA regimen

To assess the effect of PZA treatment duration (full intensive phase, partial, incomplete and no PZA treatment) upon treatment outcome, amongst MDR-TB patients with PZA strains of unknown resistance

Methods

- Medécins Sans Frontières (MSF) and the Ministry of Health, Uzbekistan, collaborated since 2003 to provide drug-resistant TB treatment within Karakalpakstan, Uzbekistan.
- Three different programme phases, reflecting changing treatment protocols (2003, 2009, 2012) (3-5).
- PZA testing was conducted on liquid media, Bactec Mycobacteria Growth Indicator Tube 960 system (BD Biosciences, Sparks, MD, USA).



Standard drugs used in MDR-TB regimens. Photo: Johanna Kuhlin.

- PZA testing conducted: 2003-2006 and 2010-2016.
- Inclusion criteria;
  (1) starting treatment between 2003-2013
  (2) microbiological diagnosis of pulmonary MDR-TB by phenotypic drug-susceptibility testing (DST)
  (3) documented treatment outcome in the programme

PZA was routinely included in MDR-TB regimens and could be stopped according to prevailing protocol; 2003 and 2009 – PZA stopped at any time if strain was PZA resistant, 2012 – PZA stopped after the intensive phase if strain was PZA resistant.

We designed a retrospective cohort study using a multivariable logistic regression analysis. The primary analysis assessed the odds ratio (OR) of a successful outcome (cure or treatment completed) amongst patients with PZA-susceptible strains compared to resistant in patients treated with PZA in the intensive phase. Throughout the analysis a successful outcome was compared with Failure/Death. The secondary analysis assessed the association between a successful outcome and PZA length of treatment, amongst patients without a diagnostic PZA DST. Power calculations for the primary analysis were performed using an OR 1.6 based on the latest meta-analysis (6), rendering a power of 40%.

Results

- 2,446 patients fulfilled the inclusion criteria
- Male 48.6% (n=1,189), median age 30.5 years (IQR 24-42)
- Patient isolates had median four resistant drugs at diagnosis (IQR 4-4) and 87.2% (n=2,132) had at least five effective drugs in their regimen during the intensive phase.
- Available PZA DST at diagnosis 34.0% (832/2,446), 73.6% (612/832) PZA resistant strains.
- Outcomes: Successful outcome 59.4%, 5.8% died, 11.9% failed and 22.9% lost to follow-up.

Table 1 Crude and adjusted analyses of effect of PZA susceptibility and other exposure variables upon treatment outcome amongst patients treated with a full intensive phase PZA regimen

	Death/Failure n (%)	Success n (%)	Crude OR (95% CI)	p value	Adjusted† OR (95% CI)	p value
	112/508* (22.0%)	396/508* (78.0%)				
Pyrazinamide						
Resistant	80 (22.2%)	280 (77.8%)	1.00			
Susceptible	32 (21.6%)	116 (78.4%)	1.04 (0.65-1.65)	0.9	0.86 (0.51-1.44)	0.6
Sex						
Female	63 (22.6%)	216 (77.4%)	1.00			
Male	49 (21.4%)	180 (78.6%)	1.07 (0.70-1.63)	0.7	1.04 (0.67-1.61)	0.9
Age						
Years, median (IQR)	32 (26.0-43.5)	30 (23.5-41.5)	0.99 (0.97-1.00)	0.06	0.99 (0.97-1.00)	0.07
TB programme						
2003	12 (20.3%)	47 (79.7%)	1.00			
2009	42 (27.1%)	113 (72.9%)	0.69 (0.33-1.42)	0.3	0.58 (0.26-1.29)	0.2
2012	58 (19.7%)	236 (80.3%)	1.04 (0.52-2.08)	0.9	0.91 (0.41-1.99)	0.8
Diabetes						
No	90 (21.5%)	328 (78.5%)	1.00			
Yes	9 (37.5%)	15 (62.5%)	0.46 (0.19-1.08)	0.07		
Unknown	13 (19.7%)	53 (80.3%)	1.12 (0.58-2.14)	0.7		
Previous 1st line drugs						
No	18 (14.8%)	104 (85.2%)	1.00			
Yes	94 (24.4%)	292 (75.6%)	0.54 (0.31-0.93)	0.03	0.55 (0.31-0.99)	0.05
Previous 2nd line drugs						
No	88 (20.4%)	344 (79.6%)	1.00			
Yes	24 (31.6%)	52 (68.4%)	0.55 (0.32-0.95)	0.03		
Cavities on X-ray						
No	26 (18.6%)	114 (81.4%)	1.00			
Yes	86 (23.4%)	282 (76.6%)	0.75 (0.46-1.22)	0.3	0.83 (0.49-1.39)	0.5
Sputum smear‡						
Negative	18 (12.9%)	121 (87.1%)	1.00			
Scanty/1+	40 (23.5%)	130 (76.5%)	0.48 (0.26-0.89)	0.02		
2+/3+	53 (26.9%)	144 (73.1%)	0.40 (0.22-0.73)	0.002		
Number of drugs to which diagnostic strain resistant						
Number, median (IQR)	4 (4-5)	4 (4-4)	0.64 (0.51-0.81)	<0.001	0.64 (0.50-0.81)	<0.001
Median potentially effective drugs in intensive phase						
2-4	24 (21.4%)	88 (78.6%)	1.00			
5-6	77 (20.5%)	298 (79.5%)	1.06 (0.63-1.77)	0.8		
7-8	11 (52.4%)	10 (47.6%)	0.25 (0.09-0.65)	0.005		

*142 patients excluded due to having no PZA treatment in full intensive phase, one patient excluded due to unknown X-ray result out of 651 patients with outcome Death/Failure/Cure/Treatment completed. †Adjusted for age, sex, previous FLD, cavities on X-ray, programme year and number of resistant drugs at diagnosis. ‡Two missing values due to unknown smear result. P-values: Wald test.

Table 2 Crude and adjusted analyses of effect of PZA regimen received upon treatment outcome amongst patients with no available PZA DST at diagnosis

	Death/ Failure n (%)	Success n (%)	Crude OR (95% CI)	p value	Adjusted† OR (95% CI)	p value
	247/1,114* (22.2%)	867/1,114* (77.8%)				
Full intensive phase PZA regimen						
Partial (<80%)	18 (18.9%)	77 (81.1%)	1.00			
Full PZA regimen (≥80%)	229 (22.5%)	790 (77.5%)	0.81 (0.47-1.38)	0.4	0.86 (0.49-1.51)	0.6
PZA treatment length in intensive phase						
None (<16%)	14 (18.4%)	62 (81.6%)	1.00			
Incomplete (≥16% and <80%)	4 (21.1%)	15 (78.9%)	0.85 (0.24-2.94)	0.8	0.80 (0.22-2.94)	0.7
Full PZA regimen (≥80%)	229 (22.5%)	790 (77.5%)	0.78 (0.43-1.42)	0.4	0.82 (0.43-1.55)	0.5

*157 excluded due to having a PZA DST not defined as diagnostic before starting treatment, four excluded that were only given PZA treatment in continuation phase and 339 excluded with outcome Loss to Follow-up out of 1,614 patients with no available PZA DST at diagnosis. † Adjusted for age, sex, previous first-line drugs, cavities on X-ray, programme year and number of resistant drugs at diagnosis. P-values: Wald test.

- **No evidence of an association between a successful outcome and PZA susceptibility in both crude (OR 1.04, 95% CI 0.65-1.65, p=0.9) and adjusted analysis (OR 0.86, 95% CI 0.51-1.44, p=0.6) amongst patients receiving a full intensive phase PZA treatment. Adjustment was made for age, sex, previous FLD, cavities on X-ray, programme year and number of resistant drugs at diagnosis**
- **No evidence of an association between successful outcome and having received a full intensive phase PZA regimen, amongst patients with no available baseline PZA DST at diagnosis (OR 0.86, 95% CI 0.49-1.51, p=0.6)**
- **Similar results were seen when comparing patients who were treated with a incomplete PZA regimen or a full intensive phase compared to no PZA treatment amongst patients with no diagnostic PZA DST.**

Conclusion

No evidence was shown of an association between a successful outcome and PZA susceptibility for MDR-TB patients treated with a full intensive phase PZA standard WHO regimen in a high MDR-TB burden setting. Furthermore, there was no evidence of a dose-response association between a successful outcome and different PZA treatment regimens in the intensive phase. The major limitations was the low power for the main analysis and the retrospective and observational nature of the study contributing to an increased risk of bias. A possible explanation for the results might be that PZA treatment mainly has its effect in shortening a regimen (7) instead of improving outcomes or that patients had sufficient likely effective drugs in their regimen. The generalisability would be limited to settings with low HIV prevalence and where there is a high background prevalence of SLD resistance.

- **This study provides provocative but insufficient evidence to warrant changing PZA treatment protocols, although the evidence relating to PZA for the WHO 2016 guideline is weak.**
- **Until further evidence emerges supporting these findings, it seems prudent to continue including PZA in standard MDR-TB regimens unless resistance is certain.**
- **We recommend research into alternative add-on agents in settings with high PZA resistance.**

Ethics

This study fulfilled the exemption criteria set by the MSF Ethics Review Board (ERB) for a posteriori analyses of routinely collected clinical data and thus did not require MSF ERB review (30). It was conducted with permission from Dr Sidney Wong (Medical Director, Operational Centre Amsterdam), MSF. It was also approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee.

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