Kuhlin, Johanna; Smith, Christopher; Khaemraev, Atadjan; Tigay, Zinaida; Parpieva, Nargiza; Tillyashaykhov, Mirzagaleb; Achar, Jay; Hajek, Jan; Greig, Jane; du Cros, Philipp; +1 more... Moore, David; (2017) The impact of pyrazinamide resistance on the treatment outcome of patients with multidrug-resistant tuberculosis in Karakalpakstan, Uzbekistan. In: Medicines Sans Frontieres Scientific Day, London. https://researchonline.lshtm.ac.uk/id/eprint/4655279 (Unpublished)

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Background

Pyrazinamide (PZA) is regarded as an important agent in the management of multidrug-resistant tuberculosis (MDR-TB) treatment (rifampicin and isoniazid) and has been shown to reduce treatment duration for drug-sensitive TB (1). Since the inclusion of PZA in an MDR-TB regimen adds significantly to both the pill burden and the side effects (mainly arthralgia and hepatotoxicity), 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.

Method

• **Medecins Sans Frontieres (MSF)** and the Ministry of Health, Uzbekistan, collaborated since 2003 to provide drug-resistant TB treatment within Karakalpakstan, Uzbekistan.
• **PZA testing** was conducted on liquid media, Bectec Mycobacteria Growth Indicator Tube 965 system (BD Biosciences, Sparks, MD, USA).
• **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 patients treated in the intensive phase of the programme. 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%.

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 effective drugs in their regimen. The generalizability would be limited in settings with low HIV prevalence and where there is a high background of SLDR resistance.

- This study provides provocative but insufficient evidence to warrant changing PZA treatment protocols, although the evidence relating to PZA for the WHO 2018 guidelines 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.

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 4-5) 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% (6/832) PZA resistant strains.
  - Outcomes: Successful outcome 59.4%, 5.8% died, 11.9% failed and 22.9% lost to follow-up.

### Table 1

<table>
<thead>
<tr>
<th><strong>Characteristic</strong></th>
<th><strong>Success (OR)</strong></th>
<th><strong>Adjusted OR (95% CI)</strong></th>
<th><strong>p value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PZA resistance</td>
<td>0.51 (0.34-0.75)</td>
<td>0.55 (0.32-0.95)</td>
<td>0.05</td>
</tr>
<tr>
<td>Sex</td>
<td>1.12 (0.58-2.14)</td>
<td>0.46 (0.19-1.08)</td>
<td>0.05</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>1.00</td>
<td>1.0</td>
</tr>
<tr>
<td>HIV prevalence</td>
<td>0.80 (0.51-1.36)</td>
<td>0.80 (0.33-2.05)</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.91 (0.41-1.99)</td>
<td>0.69 (0.22-2.03)</td>
<td>0.5</td>
</tr>
<tr>
<td>Previous 1st line drugs</td>
<td>1.6 (0.96-2.66)</td>
<td>1.00</td>
<td>1.0</td>
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<tr>
<td>Previous 2nd line drugs</td>
<td>1.00</td>
<td>1.00</td>
<td>1.0</td>
</tr>
<tr>
<td>Cavities on X-ray</td>
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<td>1.00</td>
<td>1.0</td>
</tr>
<tr>
<td>Number of drugs to which diagnostic strain resistant</td>
<td>1.00</td>
<td>1.00</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th><strong>Characteristic</strong></th>
<th><strong>Success (OR)</strong></th>
<th><strong>Adjusted OR (95% CI)</strong></th>
<th><strong>p value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PZA treatment length in intensive phase</td>
<td>0.03</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Number of drugs to which diagnostic strain resistant</td>
<td>0.03</td>
<td>0.03</td>
<td>0.05</td>
</tr>
</tbody>
</table>

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.

References


Acknowledgements

We would like to thank all the staff, both within MSF and Ministry of Health in Uzbekistan. This project is dedicated to all MDR-TB patients in Karakalpakstan, Uzbekistan, who made this study possible and to those who continue to struggle with a dreadful treatment of a curable disease.

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

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