Tuberculosis in 2017: Searching for new solutions in the face of new challenges

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Short MDR-TB Regimen, Uzbekistan

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Short MDR-TB Regimen, Uzbekistan

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Problem Statement

• WHO recommends the shorter MDR-TB treatment regimen (SCR) under specific conditions

• But is this feasible in Europe?
Overview

• Study Design

• Overall Cohort Results

• Comparison SCR vs standard of care
  – Sputum Culture conversion at 2 months
  – Outcomes 20+ months

• Implications
Background

- Karakalpakstan Population 1.7 million
- TB prevalence: 100.3/100,000
- MDR: New = 23 % Retreatment cases = 62%
- MDR-TB success rate = 57%
- Amongst MDR-TB patients
  - Ethambutol resistance = 77.1%
  - Pyrazinamide resistance = 73.6%
Short Course Study

- Single-arm prospective observational

- Standardised assessment
  - ECG, Audiometry, Visual assessment
  - GeneXpert, Hain First & Second line, smear, culture

- Ethics approval from National and MSF ERBs
Intensive Phase
4-6 Cm/Km – Mfx – Pto – Cfz – Z – H_{HD} – E

Continuation Phase
5 Mfx – Pto – Cfz – Z – E

Moxifloxacin dose = 400 mg
Eligibility

Inclusion Criteria

• RR TB patients (GeneXpert, Hain MTBDR and/or DST)
• If <14yo, confirmed close contact with RDR TB case
• Informed consent

Exclusion Criteria

• Taken Second line drugs > 1 month
• Critically ill
• Meningeal/Osteoarticular disease
• Resistance to Ofx or dual-injectables (Km/Cm) or XDR TB
• CrCl <30ml/min
• QTc >500ms
• Pregnancy
Treatment model

• Ambulatory care from diagnosis

• Social, psychological and adherence support

• Early identification and management of side-effects

• Direct observed therapy 7 days per week

• Additional ECG monitoring (baseline, 2w, 4w) for SCR

• Follow-up at 2 weeks, then monthly & 6 & 12 months post-treatment
Snapshot

• Recruited September 2013 - May 2015 in 3 Rayons

• 127 patients met inclusion and exclusion criteria

• Additional 19 patients commenced SCR but met exclusion criteria → withdrawn

• Last patients completed treatment Feb 2016

• Final follow up visits and cultures still in progress
Screened N=351

Excluded N=205

Enrolled N=146

127 Met Inclusion & Exclusion Criteria

Main Reasons Exclusion

<table>
<thead>
<tr>
<th>Reason</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of 2\textsuperscript{nd} Line drug use &gt; 1 month</td>
<td>25%</td>
</tr>
<tr>
<td>Additional resistance (Ofx, dual-injectables)</td>
<td>19%</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>11%</td>
</tr>
<tr>
<td>Lack of consent</td>
<td>17%</td>
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</tbody>
</table>

Treatment model:

ACD1 85%

Inpatient 15%
Screened N=351

Excluded N = 205

Enrolled N=146

Exclusion from study N=19

SL Drug resistance (XDR/pre-XDR) N = 16

Non-MDR (DS/PDR) N = 3

127 Met Inclusion & Exclusion Criteria

Success N=92 (72.4%)

Loss to follow-up (Default) N=12 (9.4%)

Died N=2 (1.6%)

Failure N = 21 (16.5%)
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15 microbiological
1 EPTB
5 AEs
Adverse Events

• Any adverse event 78% pts

• 1 grade 4 adverse event

• >75% adverse events grade 1 and 2

• Major adverse events: gastrointestinal, headache, arthralgia, anorexia, elevated creatinine, tinnitus/hearing loss

• Serious adverse events:
  – 15 SAEs;
  – 2 deaths
### Interim follow-up outcomes

<table>
<thead>
<tr>
<th>Follow up point</th>
<th>No. of patients</th>
<th>Completed Clinical Ax</th>
<th>Sputum not collected</th>
<th>Relapse</th>
<th>Confirmed Relapse Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>90</td>
<td>82</td>
<td>6</td>
<td>1*</td>
<td>66 culture neg (cultures results still awaited)</td>
</tr>
</tbody>
</table>

- Patient was out of country at 12 months – on return at 17 months had positive sputum culture – currently being considered as relapse.
Comparison of SCR versus Standard of Care in Uzbekistan

• Comparison of SCR with the Standard of Care

• Analysis 1 – 2 month culture conversion comparison

• Analysis 2 – SCR with 1 year follow-up and Standard of Care after 20+ months treatment

• Exclusions: 2nd line drug exposure, Km/Cm or ofloxacin resistance, EPTB
Analysis 1: 2-month culture conversion

- Short course regimen associated with higher proportion of 2-month culture conversion
  - SCR: adjusted odds ratio of 2.28 (95% CI 1.24-4.18; p=0.08)
  - Adjusted for age, gender, baseline smear
  - Baseline DST to pyrazinamide, ethambutol and kanamycin had not significant effect
Preliminary analysis 2: End of treatment outcomes

• SCR 1 year post treatment follow up (21-23 months) versus standard of care (20-24 months)

• No statistical evidence of difference between short course regimen and standard of care at 20+ months
  – aOR 1.19 (95% CI 0.71 – 2.00; p=0.498)
  – Adjusting for age, gender, baseline kanamycin resistance
  – Further analyses still in progress
In summary...

• The 2 analyses show faster culture conversion, and similar final treatment outcomes
  – For appropriately selected patients
  – Region with high rates of second-line drug resistance
Implications for scale up of the regimen
Patient selection in contexts with high second line drug resistance

• Not suitable for all patients
  – 35-50% patients eligible in this context

• Importance of adherence support for commencing ambulatory treatment from day 1
Patient selection in contexts with high second line drug resistance

• What to do with Z or Km resistance?

  – Preliminary analysis suggests could still use, but may be prudent to await more data on Km resistance

  – An option – wait for full DST results and then switch patients to SCR
Management of patients failing the regimen

• If failing regimen
  – 4-6 Cm/Km – Mfx – Pto – Cfz – Z – $H_{HD}$ – E

• Likely effective drugs
  – (Injectable), Cs, Lzd, Bdq, Dld, Imp/Clv, PAS
Conclusions

• Good end-of-treatment and interim follow-up outcomes in selected group of patients

• Adverse events and LTFU in this study highlight importance of adherence support management
Conclusions

- SCR achieves faster sputum culture conversion
- SCR has low relapse rate
- Roll out SCR in high SLD resistance context requires molecular test lab capacity and roll out of Group C and D drugs
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