Adverse effects of routine second-line antituberculosis drugs and bedaquiline in children with multidrug-resistant tuberculosis

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February 7, 2017
Introduction

- **Aim** – review common and important adverse effects of 2\textsuperscript{nd}-line TB drugs and bedaquiline in children
  - Practical, clinical considerations
  - Not touching on IMPAACT-specific reporting processes

- **Ground rules**
  - Okay to as questions during the presentation
  - Would like to hear your experience
Overview

- General considerations for AE assessment in children
- Common and important AEs of 2\textsuperscript{nd}-line TB drugs by drug class
- Bedaquiline AEs
- Toxicity management – P1108
- Conclusion
General considerations (1)

- Why important?
  - Complex multidrug-regimens
  - Clinical management
  - Assessment of attribution in context of trial

- Fewer adverse effects in children vs adults
  - Actually tolerate better?
  - Lower drug exposures
  - Difficulty in assessing subjective effects, under-reporting (??)
General considerations (2)

- “My ore het toegeslaan” – My ears were blocked
- “Long was seer en water” - Lung was sore and water (in my lung)
- “Jeuk” - Itch
- “My maag was altyd seer” - My stomach always pained
- “Bene was altyd seer van die naald” - Legs always pained from the needle (injection)
- “Ek raak lam in my bene van die medikasie” - I become weak in my legs from the medication
- Ek kan nie ver loop nie” - I cannot walk far
- My voete was seer as ek loop”- My feet were hurting when I walk
Resources

**REVIEW**

**Adverse effects of oral second-line antituberculosis drugs in children**

H. Simon Schaaf\textsuperscript{a}, Stephanie Thee\textsuperscript{b}, Louvina van der Laan\textsuperscript{a}, Anneke C. Hesseling\textsuperscript{a} and Anthony J. Garcia-Prats\textsuperscript{a}

\textsuperscript{a}Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; \textsuperscript{b}Department of Paediatric Pneumology and Immunology, Charité, Universitätsmedizin Berlin, Berlin, Germany

**REVIEW**

**The safety and tolerability of the second-line injectable antituberculosis drugs in children**

Anthony J. Garcia-Prats, H. Simon Schaaf and Anneke C. Hesseling

Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa
# WHO Revised grouping of MDR-TB medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Fluoroquinolones</td>
<td>Levofloxacin, Moxifloxacin, Gatifloxacin</td>
</tr>
<tr>
<td>B. Second-line injectables</td>
<td>Amikacin, Capreomycin, Kanamycin</td>
</tr>
<tr>
<td>C. Other core second-line agents</td>
<td>Ethionamide/prothionamide, Cycloserine/terizidone, Linezolid, Clofazimine</td>
</tr>
</tbody>
</table>
Flouroquinolones (1)

- **Musculoskeletal**
  - Arthropathy, achilles tendon rupture
  - Animal data
  - Clinical experience in children
    - Minimal, non-severe, self-limited
    - No reported cases of achilles tendon rupture

- **Cardiac**
  - QT interval prolongation
  - Mfx > Lfx
  - Limited experience in children
Flouroquinolones (2)

- Central nervous system
  - Caffeine-like effects – sleep disturbance, hyperactivity
  - Nightmares, hallucinations
  - Intracranial hypertension
  - Management

- Others
  - Dermatologic
  - GI disturbance
  - Ophthalmologic
## MDRPK1: Baseline characteristics (n=70)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (range)</td>
<td>2.1 (0.4-7.3)</td>
</tr>
<tr>
<td>Age at enrolment</td>
<td></td>
</tr>
<tr>
<td>0 to &lt;2 years</td>
<td>31 (44%)</td>
</tr>
<tr>
<td>2 to &lt;6 years</td>
<td>35 (50%)</td>
</tr>
<tr>
<td>6 to &lt;15 years</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Male sex</td>
<td>38 (54%)</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>12 (17%)</td>
</tr>
<tr>
<td>Weight-for-age Z-score &lt; -2</td>
<td>16 (23%)</td>
</tr>
<tr>
<td>Person-years of observation</td>
<td></td>
</tr>
<tr>
<td>Total, in years</td>
<td>68.5</td>
</tr>
<tr>
<td>Median, in months (IQR)</td>
<td>11.6 (9.2-14.7)</td>
</tr>
</tbody>
</table>
## Results (1): All adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th># of patients with event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>total # of events</th>
<th>Event Rate (per person-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.044</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Pain other than traumatic injury</td>
<td>11</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>0.161</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0.073</td>
</tr>
<tr>
<td>Neurosensory alteration</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.015</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.015</td>
</tr>
<tr>
<td>Fatigue/malaise</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.015</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>0.190</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>23</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td>0.351</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>0.190</td>
</tr>
<tr>
<td>Cutaneous reaction</td>
<td>12</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>0.204</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>0.248</td>
</tr>
<tr>
<td>Acute systemic allergic reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>ALT</td>
<td>22</td>
<td>17</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>27</td>
<td>0.394</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>

# of events may exceed # of patients with event, as patients may have had more than one event.
Results (2): Adverse effects at least possibly related to levofloxacin

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th># of patients with event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>total # of events</th>
<th>Event Rate (per person-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.029</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Pain other than traumatic injury</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0.058</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0.029</td>
</tr>
<tr>
<td>Neurosensory alteration</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.015</td>
</tr>
<tr>
<td>Fatigue/malaise</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>0.131</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>0.234</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0.102</td>
</tr>
<tr>
<td>Cutaneous reaction</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0.102</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0.117</td>
</tr>
<tr>
<td>Acute systemic allergic reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>ALT</td>
<td>16</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>0.263</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>

# of events may exceed # of patients with event, as patients may have had more than one event
Second-line injectables (1)

- **Nephrotoxicity**
  - Renal tubular dysfunction, oliguric renal failure
  - Adults - <1 – 9.8%
  - Children – unusual
  - Capreomycin – may pose higher risk

- **Electrolyte abnormalities**
  - Hypokalemia, hypomagnesemia
  - Capreomycin
  - Adults – up to 35%, cohort in Peru
  - Children - unusual
Second-line injectables (2)

- Ototoxicity
  - Up to 25% in children*
  - Permanent sensorineural
  - High frequency hearing loss most common
  - HL may continue after stopping the drug
  - Risks
    - Cumulative drug exposure
    - Genetics,
    - Agent (??)
Second-line injectables (3)

- Ototoxicity (cont).

- How to assess
  - Pure tone audiometry
  - Otoacoustic Emission (OAE)
    - Ensure can test high frequencies

- Assess middle ear via tympanometry or otoscopy (conductive hearing loss)
  - Interpret OAE/pure tone in light of these results.

- Routinely screen for hearing abnormality
  - Cannot rely on subjective report of hearing loss or gross evidence of hearing loss
  - Baseline, then monthly
  - If abnormal then more frequent

- Management
Second-line injectables (4)

- Injection site adverse effects
  - Local irritation/redness
  - Subcutaneous and muscles abscesses
  - Infection
  - Neurovascular injury
  - Fibrosis

- Injection pain
  - Co-administration with lignocaine
Ethionamide/prothionamide (1)

- GIT disturbances
  - Poor palatability - metallic taste
  - Nausea, vomiting
    - May need to split dose or start with lower dose, but usually stops within 1-2 weeks

- Hepatotoxicity

- Other less common:
  - Convulsions
  - Peripheral neuropathy – pyridoxine responsive
  - Gynaecomastia
Ethionamide/prothionamide (2)

- Retrospective cohort, 137 children on a regimen containing ethionamide:
- Abnormal TFTs - 79 of 137 (58%) Elevated serum TSH and suppressed fT4 in 30 (22%)
- Risk of hypothyroidism higher with treatment with PAS and in HIV-infected children.
Ethionamide/prothionamide (3)

- **Screening**
  - Symptomatic hypothyroidism uncommon
  - Interpret with caution in first 1-2 months of treatment - acute illness may affect TFTs

- **Management**
  - If primary hypothyroidism (elevated TSH, low fT4), supplement with levothyroxine (50 mcg OD)
  - Reversible - stop levothyroxine once ETO/PAS stopped
Cycloserine/terizidone

- Neurological system AEs:
  - Dose-related
  - Dizziness, insomnia, headache, tremor, anxiety, confusion, depression, psychosis, convulsions
  - Adults – 9.1%
  - Children – infrequent (??)

- Pyridoxine supplementation should be prescribed

- Management
  - Reduce the dose or stop the drug if CNS AEs occur
  - Treatment of psychiatric events
Linezolid (1)

- General
  - Adult SR-MA (n=107)
    - 59% experienced linezolid-related AE
    - 69% of these required dose reduction or discontinuation
  - Dose and duration dependent
  - Many related to inhibition of mitochondrial protein synthesis
Linezolid (2)

- Neurologic
  - Peripheral neuropathy (47%)
  - Optic neuropathy (13%)

- Haematologic
  - Anaemia (38%)
  - Thrombocytopenia (12%)

- Other – lactic acidosis, pancreatitis, rhabdomyolysis

- Children – less frequent, but still problematic

- Management
  - Dose reduction or discontinuation
Clofazimine

- **Gastrointestinal** – nausea, vomiting, pain
- **Dermatologic**
  - Skin discoloration
    - Reddish, black, orange
    - Resolves slowly over time
  - Icthyosis
    - Thickened, dry, scaly skin
    - Up to 25%, but highly variable in reports
- **Cardiac**
  - QT interval prolongation
Para-aminosalicylic acid (PAS)

- GIT disturbances
  - Anorexia, diarrhoea, nausea
  - Relatively well tolerated in our experience
- Hypothyroidism
  - Risk quite high (79% in one small study)
  - Increased risk with ethionamide co-treatment
- Hepatotoxicity
**Bedaquiline (1)**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use SIRTURO™ safely and effectively. See full prescribing information for SIRTURO.

SIRTURO™ (bedaquiline) Tablets
Initial U.S. Approval – 2012

**WARNINGS:**

*See Full Prescribing Information for complete boxed warning.*

- An increased risk of death was seen in the SIRTURO treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO when an effective treatment regimen cannot otherwise be provided.
- QT prolongation can occur with SIRTURO. Use with drugs that prolong the QT interval may cause additive QT prolongation.
Bedaquiline (2)

- Most common AEs
  - Nausea
  - Arthralgia
  - Headache

- Liver abnormalities
  - Increased risk with BDQ vs placebo
    - ALT >3x ULN – BDQ 10.8% vs placebo 5.7%
  - Mostly mild, self-limited
Bedaquiline (3)

- Cardiac - QT prolongation
  - Correlate with cumulative drug exposure – peak 16-18 weeks
  - Study 1 - QTcF change from baseline
    - 15.7ms (BDQ) vs 6.2ms (PLB) – week 18
  - Study 3 – QTcF change from baseline
    - No other QT prolonging drugs – 23.8ms, 0 > 480ms
    - 2 other QT prolonging drugs – 30.7ms, 1 > 500ms
  - No Torsade de Pointes
  - Risk factors – electrolyte abnormalities, hypothyroidism
## APPENDIX V: SUPPLEMENTAL TOXICITY TABLE FOR GRADING ELECTROCARDIOGRAM CHANGES AND POSSIBLE SYMPTOMS RELATED TO CARDIAC CONDUCTION ABNORMALITIES

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG Criteria:</strong></td>
<td>ECG Criteria: corrected QTc interval</td>
<td>ECG Criteria: corrected QTc interval</td>
<td>ECG Criteria: corrected QTc interval</td>
<td>ECG Criteria: corrected QTc interval</td>
</tr>
<tr>
<td>Note: QT corrected based on Frederic method (QTc=QT/cubed root of RR interval).</td>
<td>QTc ≥460msec, but &lt;480msec</td>
<td>QTc ≥480msec, but &lt;500msec</td>
<td>QTc ≥500msec OR QT &gt; 60 msec greater than baseline AND QT ≥480 ms</td>
<td>Life-threatening consequences (Torsades de pointes, other serious ventricular dysrhythmias)</td>
</tr>
<tr>
<td><strong>Cardiac Clinical Criteria</strong></td>
<td>Any one of the following clinical symptoms (one event, without clear evidence of non-cardiac etiology):</td>
<td>Any one of the following clinical symptoms (one event, without clear evidence of non-cardiac etiology):</td>
<td>Any one of the following clinical symptoms (one event, without clear evidence of non-cardiac etiology):</td>
<td>Any one of the following clinical symptoms (one event, without clear evidence of non-cardiac etiology):</td>
</tr>
<tr>
<td></td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
</tr>
<tr>
<td></td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
</tr>
<tr>
<td></td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
</tr>
<tr>
<td></td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
</tr>
<tr>
<td><strong>Clinical Signs</strong></td>
<td>Recurrence/ongoing recurrent clinical symptoms with evidence of ventricular tachycardia:</td>
<td>Recurrence/ongoing recurrent clinical symptoms with evidence of ventricular tachycardia:</td>
<td>Recurrence/ongoing recurrent clinical symptoms with evidence of ventricular tachycardia:</td>
<td>Recurrence/ongoing recurrent clinical symptoms with evidence of ventricular tachycardia:</td>
</tr>
<tr>
<td></td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
</tr>
<tr>
<td></td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
</tr>
<tr>
<td></td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
</tr>
<tr>
<td></td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
</tr>
<tr>
<td><strong>Note</strong></td>
<td><em>Note that this presence of Ventricular Tachycardia (VT) is the adverse outcome to be avoided/identified; the symptoms are surrogates for “possible” VT, but if VT is demonstrated, then BDQ is permanently discontinued irrespective of QTc or symptoms.</em></td>
<td><em>Note that this presence of Ventricular Tachycardia (VT) is the adverse outcome to be avoided/identified; the symptoms are surrogates for “possible” VT, but if VT is demonstrated, then BDQ is permanently discontinued irrespective of QTc or symptoms.</em></td>
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</tr>
</tbody>
</table>
## APPENDIX VI: TOXICITY MANAGEMENT OF SPECIFIC TOXICITIES
### ECG-Determined or Clinical Cardiac Toxicity

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Continue BDQ</td>
<td>Repeat ECG and clinical evaluation of symptoms within 72 hours</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue BDQ</td>
<td>Repeat ECG and clinical evaluation of symptoms within 48 hours</td>
</tr>
<tr>
<td>Grade 3 (ECG)</td>
<td>Hold Fluoroquinolone (FQ) and BDQ</td>
<td>If repeat ECG and clinical evaluation of symptoms within 72 hours continues to show Grade 3, hold the FQ and hold study drug (= Grade 4). Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary. Contact the study team and indicate in the participant line: “Grade 3 ECG.”</td>
</tr>
<tr>
<td>Grade 3/4 (Cardiac Clinical Criteria)</td>
<td>Hold FQ and Permanently discontinue BDQ if not other explanation; e.g., lab abnormality</td>
<td>Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary. Contact the study team and indicate in the participant line: “Grade 3/4 Cardiac.” Discuss with the team the permanent discontinuation of study drug.</td>
</tr>
<tr>
<td>Grade 4 (ECG)</td>
<td>Hold FQ and Permanently discontinue BDQ if not other explanation; e.g., lab abnormality</td>
<td>Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary. Contact the study team and indicate in the participant line: “Grade 4 ECG.” Discuss with the team the permanent discontinuation of study drug.</td>
</tr>
</tbody>
</table>

*Note: STUDY DRUG USE for Cardiac Clinical Criteria meeting Grade 3 or Grade 4 are equivalent – that is permanently discontinue BDQ.*
**APPENDIX VIII: TOXICITY MANAGEMENT OF GENERAL TOXICITIES**

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Continue BDQ</td>
<td>Routine monitoring</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue BDQ</td>
<td>Monitor closely with more frequent visits; as per site clinician, work-up to exclude other causes.</td>
</tr>
<tr>
<td>Grade 3 – confirmation pending</td>
<td>Hold BDQ while awaiting confirmation of Grade 3 toxicity unless clinician believes that resuming BDQ will be unsafe and so elects to permanently discontinue.</td>
<td>Contact the study team upon determination of any Grade 3 or 4 toxicity. Indicate in the participant line P1108, grade and type of toxicity.</td>
</tr>
<tr>
<td>Grade 3 – confirmed and presumed, possibly, probably, or definitely related to BDQ</td>
<td>Permanently discontinue BDQ</td>
<td>The participant should be monitored closely until resolution to &lt; Grade 2. As per site clinician, work-up to exclude other causes. Contact the study team upon confirmation of Grade 3 toxicity. Indicate in the participant line: P1108 Grade 3 and specify the toxicity.</td>
</tr>
<tr>
<td>Grade 4 and presumed, possibly, probably, or definitely related to BDQ</td>
<td>Permanently discontinue BDQ</td>
<td>Participants should be monitored closely with more frequent visits until resolution to &lt; Grade 2. Contact the study team upon determination of Grade 4 toxicity. Indicate in the participant line: P1108 Grade 4 and specify the toxicity.</td>
</tr>
</tbody>
</table>
### Toxicity Management (4)

**Toxicity Management of Specific Toxicities: Lactate**

<table>
<thead>
<tr>
<th>Elevation in Lactate</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate &lt;3mmol/L</td>
<td></td>
<td>Consider the test negative.</td>
</tr>
<tr>
<td>Lactate &gt;3mmol/L</td>
<td></td>
<td>Draw additional blood sample for repeat lactate (see LPC).</td>
</tr>
<tr>
<td>If repeat lactate is &gt;3mmol/L</td>
<td>Hold Bedaquiline if mitochondrial dysfunction is suspected (based on overall clinical picture). If another underlying condition is suspected or confirmed, Bedaquiline may be continued based on clinical justification and in discussion with the protocol team.</td>
<td>Send sample for lactate/pyruvate ratio. Correlate with subject’s clinical status and contact the study team.</td>
</tr>
<tr>
<td>If repeat lactate is &lt;3mmol/L</td>
<td>Continue Bedaquiline.</td>
<td>Consider the test negative; manage based on clinical grounds.</td>
</tr>
</tbody>
</table>
Conclusion

- Questions or comments?
- Acknowledgements – Simon Schaaf