TBnet Survey: Monitoring the QT interval and new TB drugs

Introduction

This survey is on the management of QT interval prolongation in the treatment of multidrug-resistant (MDR) / extensively drug-resistant (XDR) tuberculosis and the use of the new drugs bedaquiline and delamanid. Before starting, it will be worth checking how many patients were treated with bedaquiline and delamanid at your centre. Please verify if other physicians from your centre are going to participate to this survey and cross-check the entered data with them in order to avoid double-reporting.

Thank you very much for your collaboration.

Matt Burman
Lorenzo Guglielmetti
Simon Tiberi

Part 1. General information

1. Please enter your name, e-mail address and affiliation

   Name: _______________________
   E-mail address: _______________________
   Affiliation: _______________________

2. What country are you based in?

   ______________________________________

3. What type of setting do you work in?

   □ Local/District General Hospital
   □ Regional Hospital
   □ Teaching/University Hospital
   □ TB Reference/TB Hospital
   □ Other (please precise: _________________)

4. Do you measure the QT interval in your centre (multiple answers possible)?
☐ Yes, I measure the uncorrected QT interval
☐ Yes, I measure the QTcB (QT interval corrected according to Bazett’s formula)
☐ Yes, I measure the QTcF (QT interval corrected according to Fridericia’s formula)
☐ Yes, I measure the QT but I don’t know if it is corrected or not, or which correction is used
☐ No, I don’t measure the QT interval (if this is the case, please skip all following QT-related questions)
☐ Other: please specify ______________________

5. Which specific non-antituberculosis drugs do you monitor for QTc interval prolongation?

☐ Macrolides (i.e. clarithromycin) (yes/no/don’t know)
☐ Anti-fungals (i.e. ketoconazole, fluconazole) (yes/no/don’t know)
☐ Antipsychotics (i.e. haloperidol, chlorpromazine) (yes/no/don’t know)
☐ Anti-nausea drugs (i.e. metoclopramide, ondansetron/granisetron, domperidone) (yes/no/don’t know)
☐ Opioids (i.e. methadone) (yes/no/don’t know)
☐ Antiretrovirals (i.e. atazanavir, ritonavir) (yes/no/don’t know)
☐ Others: please specify_____________________

6. When do you measure it in MDR-TB patients (choose all that are appropriate)?

☐ Before starting any QT-prolonging drug
☐ At the expected peak concentration of the drug (90-120 minutes after administration)
☐ Other: please specify___________________________

7. Do you perform regular measures of the QTc interval during treatment of MDR-TB patients?

☐ Yes
☐ No
☐ Only for patients receiving Bedaquiline and/or Delamanid
☐ In another specific group (please specify): ____________________________

8. When would you consider using Bedaquiline (multiple answers are possible)?

☐ As first-line treatment for MDR regimen (first MDR regimen cycle)
☐ As a second cycle salvage MDR regimen (previously failed patients)
☐ When there is quinolone resistance
☐ To provide an aminoglycoside sparing regimen
To give patients 4 or 5 effective drugs (where there is resistance or intolerance to other agents)
Other: please specify ________________________________

9. When would you consider using Delamanid?

☐ As first-line treatment for MDR regimen (first MDR regimen cycle)
☐ As a second cycle salvage MDR regimen (previously failed patients)
☐ When there is quinolone resistance
☐ To provide an aminoglycoside sparing regimen
☐ To give patients 4 or 5 effective drugs (where there is resistance or intolerance to other agents)
☐ Other: please state ________________________________

10. What do you use as a reference when treating patients with MDR-TB?

☐ http://www.tbdrugmonographs.co.uk/
☐ The WHO Companion Handbook for the management of drug-resistant tuberculosis
☐ National guidelines
☐ The TBnet Consensus Statement on the management of patients with MDR/XDR-TB in Europe
☐ No specific guidance
☐ Other, please specify: ________________________________
Part 2. Experience with the new drugs

A. Bedaquiline

1. Do you have experience of using Bedaquiline in Multi-Drug Resistant/XDR Tuberculosis? (if no, skip completely the section)
   ☐ Yes
   ☐ No

2. Through which mechanism do you have access to Bedaquiline (pick all that apply)?
   ☐ Compassionate use program
   ☐ Expanded access program
   ☐ The drug is registered/licensed/approved for use in my country
   ☐ Clinical trials
   ☐ Other: please specify __________________________

3. How many patients have been treated with Bedaquiline at your centre?
   _____

4. Do you require approval from another health body/organisation to use it?
   ☐ Yes
   ☐ No

5. If yes, which organisation gives you approval to use Bedaquiline?
   ☐ Physician choice
   ☐ Local/Hospital Level
   ☐ MDR Cohort Review
   ☐ Advisory Group/National Consilium
   ☐ ERS/WHO Consilium
   ☐ Other: please specify __________________________

6. What side effects have you noted in patients on treatment with Bedaquiline?
   Common:
   ☐ Arthralgia
☐ Chest pain
☐ Gastrointestinal: Nausea
☐ Neurological: Headache
☐ Respiratory: Haemoptysis

**Serious:**
☐ Liver Enzyme Abnormalities
☐ Pancreatitis
☐ Prolonged QTc
☐ Arrhythmia
☐ Other: please specify ____________________________

7. What specific monitoring do you use during treatment with Bedaquiline, in addition to standard treatment monitoring?

☐ ECG
☐ LFTs
☐ Lipase
☐ Albumin
☐ Urea and electrolytes, calcium & magnesium
☐ Other: please specify ____________________________

8. How frequently do you monitor ECGs?

☐ At Baseline
☐ Daily
☐ Weekly
☐ Monthly
☐ Other: please specify ____________________________

9. Did you ever have to permanently stop Bedaquiline treatment because of cardiac side-effects/prolonged QTc?

☐ Yes
☐ No
If yes, in how many patients: ____________________________

10. If stopping Bedaquiline treatment because of a cardiac side-effect/prolonged QTc, what criteria do you use?

☐ An increase in QTc from baseline of more than 20ms (yes/no/don’t know)
☐ Any QTc values greater than 470ms in women / 450ms in men (grey area before significant increase)
11. Have any of your patients experienced a cardiac event (e.g., atrial fibrillation, syncope, Torsade de Pointes, palpitations) whilst on Bedaquiline?

☐ Yes
☐ No

12. If yes:
   How many patients? ____________________
   If yes, what was the patient's QTc (at baseline and at the moment of the event):
   ____________________
   If yes, which other drugs was the patient/patients receiving: ____________________
   If yes, did the patient/patients have any risk factors for arrhythmias (e.g., congestive heart failure, electrolyte imbalance, long QT syndrome): ____________________

13. For how long do you routinely treat patients with Bedaquiline (in Months)?

☐ 3 Months
☐ 6 Months
☐ 9 Months
☐ 12 Months
☐ 18 months
☐ All treatment duration
☐ Other: please specify______________________________

14. What is the longest duration of Bedaquiline treatment you have provided (in months)?

☐ 6 months
☐ 9 months
☐ 12 months
☐ 20 months
☐ Other ____________ (please state)

15. Have you used Bedaquiline in combination with other QT-prolonging drugs (Moxifloxacin, Clofazimine, macrolides [i.e., Clarithromycin] or antiretrovirals [i.e., Atazanavir, Ritonavir])?

☐ Yes, Bedaquiline in association with one QT-prolonging drug
☐ Yes, Bedaquiline in association with two QT-prolonging drugs
☐ Yes, Bedaquiline in association with three or more QT-prolonging drugs
☐ No

16. If you did use Moxifloxacin and Bedaquiline together, which dose of Moxifloxacin did you use?

☐ 800 mg daily
☐ 400 mg daily
☐ Other, please specify : __________________________
B. *Delamanid*

1. Do you have experience of using Delamanid in Multi-Drug Resistant/XDR Tuberculosis? (if no, skip section)
   - ☐ Yes
   - ☐ No

2. Through which mechanism do you have access to Delamanid?
   - ☐ Compassionate use program
   - ☐ Expanded access program
   - ☐ The drug is registered/licensed/approved for use in my country
   - ☐ Clinical trials
   - ☐ Other: please specify _______________________

3. How many patients have been treated with Delamanid at your centre?
   ______

4. Do you require approval from another health body/organisation to use it?
   - ☐ Yes
   - ☐ No

5. Which organisation gives you approval to use Delamanid?
   - ☐ Physician choice
   - ☐ Local/Hospital Level
   - ☐ MDR Cohort Review
   - ☐ Advisory Group/National Consilium
   - ☐ ERS/WHO Consilium
   - ☐ Other: please specify _______________________

6. What side effects have you noted in patients on treatment with Delamanid?
   - ☐ Haematological
   - ☐ Hepatic: Liver Enzyme Abnormalities
   - ☐ Metabolic: Hypertrygliceridaemia, Hypercholesterolaemia
   - ☐ Psychiatric
   - ☐ Cardiovascular: Syncope, Prolonged QTC, Arrhythmia
7. What specific monitoring do you use during treatment with Delamanid, in addition to standard treatment monitoring?

☐ ECG  ☐ LFTs  ☐ Lipase  ☐ Albumin  ☐ Urea and electrolytes, calcium & magnesium  ☐ Other: please specify ________________

8. How frequently do you monitor ECGs?

☐ At Baseline  ☐ Daily  ☐ Weekly  ☐ Monthly  ☐ Other: please specify _______________________

9. Did you ever have to permanently stop Delamanid treatment because of cardiac side-effects/prolonged QTc?

☐ Yes  ☐ No
If yes, in how many patients: _______________________

10. If stopping Delamanid treatment because of a cardiac side-effect/prolonged QTc, what criteria do you use?

☐ An increase in QTc from baseline of more than 20ms (yes/no/don’t know)
☐ Any QTc values greater than 470ms in women / 450ms in men (grey area before significant increase)
☐ Only significantly increased QTc values (greater than 500ms) (yes/no/don’t know)
☐ Any QTc with symptoms (syncope, arrhythmia) (yes/no/don’t know)
☐ Other: please specify _______________________

11. Have any of your patients experienced a cardiac event (eg atrial fibrillation, syncope, Torsade de Pointes, palpitations) whilst on Delamanid?

☐ Yes
12. If yes:
How many patients? ____________________
If yes, what was the patient QTc (at baseline and at the moment of the event):
_____________________
If yes, which other drugs was the patient / patients receiving: _____________________
If yes, did the patient / patients have any risk factors for arrhythmias (eg congestive heart failure, electrolyte imbalance, long QT syndrome): _____________________

13. For how long do you routinely treat patients with Delamanid (in Months)?
☐ 3 Months
☐ 6 Months
☐ 9 Months
☐ 12 Months
☐ 18 Months
☐ All treatment duration
☐ Other: please specify ________________________

14. What is the longest duration of Delamanid treatment you have provided (in months)?
☐ 6 months
☐ 9 months
☐ 12 months
☐ 20 months
☐ Other _____________ (please state)

15. Have you used Delamanid in combination with other QT-prolonging drugs (Moxifloxacin, Clofazimine, macrolides [i.e. Clarithromycin] or antiretrovirals[i.e. Atazanavir, Ritonavir])?
☐ Yes, Delamanid in association with one QT-prolonging drug
☐ Yes, Delamanid in association with two QT-prolonging drugs
☐ Yes, Delamanid in association with three or more QT-prolonging drugs
☐ No

16. If you did use Moxifloxacin and Delamanid together, which dose of Moxifloxacin did you use?
☐ 800 mg daily
☐ 400 mg daily
☐ Other, please specify: __________________
C. Combination Therapy/Other

1. Have you ever treated patients with Delamanid and Bedaquiline in combination?
   - ☐ Yes
   - ☐ No
   If yes, how many? _______________________

2. Have you ever treated patients with Delamanid and Bedaquiline sequentially (one after the other)?
   - ☐ Yes, Bedaquiline and then Delamanid
   - ☐ Yes, Delamanid and then Bedaquiline
   - ☐ Yes, both
   - ☐ No
   If yes, how many? _______________________

3. If you did use the two drugs sequentially, how long did you wait before switching from one drug to the other (multiple answers possible)?
   - ☐ Five days before switching from Delamanid to Bedaquiline
   - ☐ Six months before switching from Bedaquiline to Delamanid
   - ☐ Other: please specify______________________
D. Conclusion

Thank you very much for your participation. Would you be interested in being contacted in order to contribute with individual patient data (age and sex, QTc values, cardiac risk factors, drugs received) to a second stage of this survey?
Centres participating in the second stage of the survey will have the opportunity to co-author any publications that result from the survey, according to ICMJE criteria for authorship. For the purposes of fairness, authors would be listed in the order that they submit their data and not only the number of cases contributed.

☐ Yes
☐ No