Using delamanid in MDR-TB

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A new anti-TB drug

- Nitro-dihydro-imidazo-oxazole derivative
- Mechanism of action
  - Inhibits M*tb* cell wall synthesis
  - Highly active against intracellular M*tb* in macrophages
- No cross-resistance with any anti-TB drugs
- Pharmacology
  - Half life 38 hours
  - Metabolized by cytochrome enzymes (CYPA4)
  - Metabolites regulated by plasma albumin

- Can prolong the QT interval (mean increase 14.4 ms, max. at 8 weeks)
- Belongs to Group 5 drugs

Conditionally approved by EMA in November 2013

Dosage and presentation

Presentation

50 mg tablets in packs of 40 film-coated tablets in aluminium blisters

Dosage

- 100 mg twice daily (200 mg total daily dose) 7 days per week for 24 weeks
- Can be taken at the same time as the other anti-TB drugs
- Should be taken with a light meal

WHO interim guidance*

MDR-TB patients in whom delamanid may have a particular role include :

- Patients with additional resistance or intolerance to quinolones or injectable drugs and patients with XDR-TB
- Patients with extensive lesions and advanced disease
- Other patients deemed at higher risk for poor outcomes

The use of the drug in patients with extra-pulmonary MDR-TB may be considered, extrapolating from the data in patients with pulmonary TB.

Conditional recommendation, very low confidence in estimates of the effects (as for Bedaquiline)

* http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf?ua=1&ua=1

endTB guidance

- Indications/contraindications
- How to construct a regimen?
- How to chose between bedaquiline and delamanid?
- Patient's monitoring

Indications

I. Patients for whom the construction of a regimen with 4 likely effective SLD including a FQ and an injectable is not possible

a. XDR-TB (resistance to FQ and at least one injectable)

b. Pre-XDR-TB (resistance to FQ or injectables)

c. Patients with two or more Group 4 drugs (Eto/Pto, Cs, PAS) compromised

d. Contact with a patient with a strain with resistance pattern of a, b, or c.

e. Patients unable to tolerate MDR-TB drugs necessary for construction of the regimen

f. Patients who are a "failure" of an MDR-TB regimen by WHO 2013 definitions

II. Other patients with high risk of unfavorable outcome

a. Patients with extensive or advanced disease (multiple cavities, bilateral lesions, or extensive parenchymal damage or multiple system involvement)

b. Patients with increased likelihood of treatment failure, or death (patients with low body mass index, HIV, diabetes, etc.)

c. Patients coming from catchment areas that have poor MDR-TB treatment outcomes despite good programmatic conditions (e.g. sites with extensive second-line drug resistance background)

Contra-indications

Absolute

- Known hypersensitivity to the drug
- Baseline ECG demonstrating a QTcF > 500 ms (repeated); or history of syncopal episodes, ventricular arrhythmias or severe coronary artery disease
- Serum albumin < 2.8 g/dL
- Refuse to consent

Relative

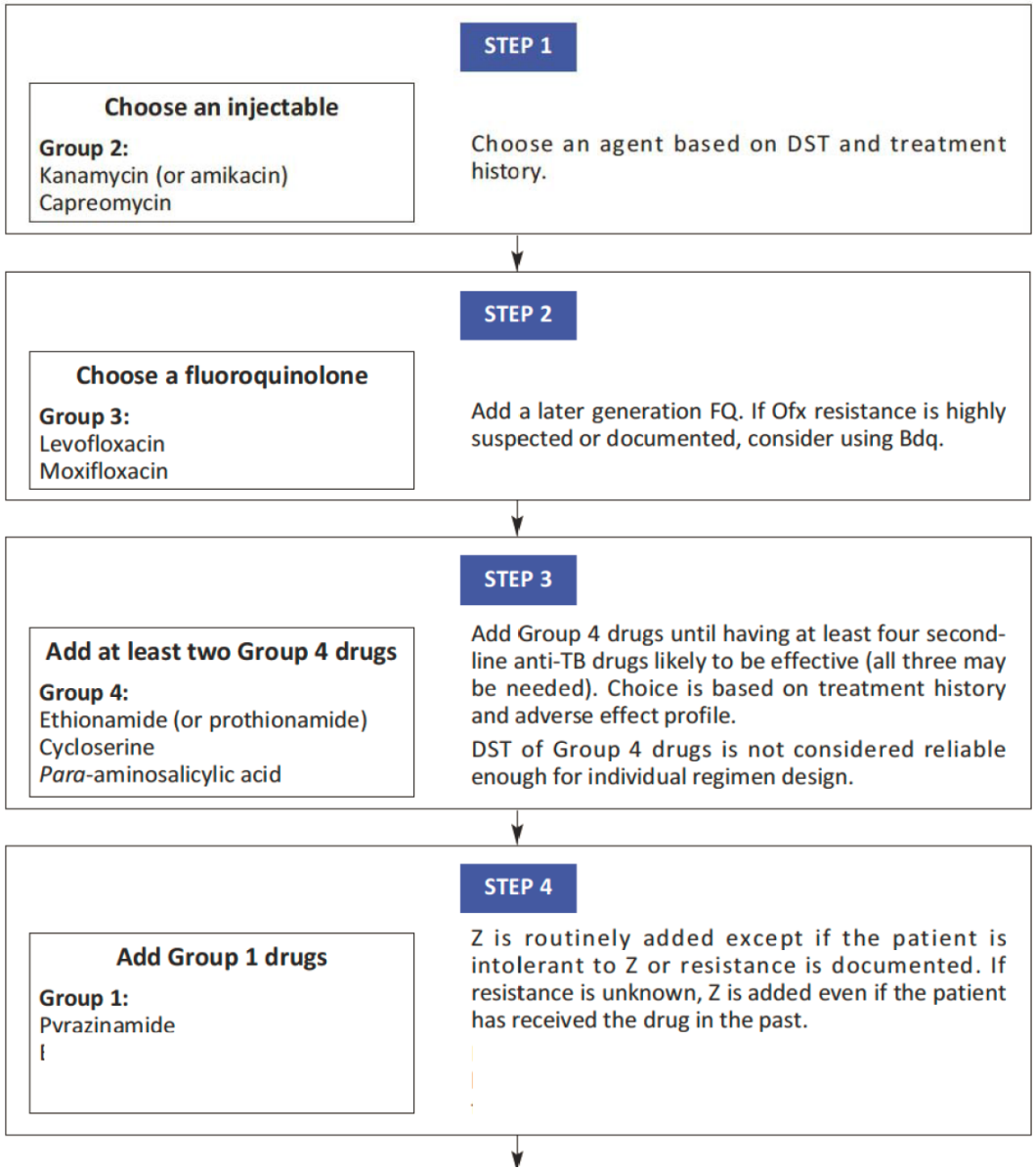
- Children <18 years
- Pregnancy and lactation

Caution

- When used with other QT prolonging drugs (Mfx, Cfz, LPV/r, ondansetron)
- When used strong inducers or inhibitors of the CYPA4
- No data on concommitant use with Bdq

How to construct a regimen?

Building a regimen



Building a regimen

STEP 5

Consider Group 5

Group 5:
Delamanid
Bedaquiline
Linezolid
Clofazimine
Imipenem/Cilastatin (plus Amx/Clv)
High dose-isoniazid
Amoxicillin/Clavulanic acid

Add Bdq or Dlm and other Group 5 drugs as needed so that there are at least four (preferably five) likely effective SLD:

. Bdq or Dlm are the Group 5 drugs of choice
. Then add Lzd, Cfz, and Imp/Cln (in that order)
. High dose H is never counted as a core drug
. The total number of Group 5 drugs is influenced by the number of Group 4 drugs considered effective

Delamanid may be added in patients with increased risk of unfavorable outcome

How to chose between bedaquiline and delamanid?

Factors to be taken in consideration

- Currently more experience with use of Bdq in XDR-TB than Dlm
- Long half-life of Bdq (5 months) :
  - Dlm cannot be used after Bdq before a wash out period of 6 months
  - Risk of potential monotherapy to Bdq when the treatment is stopped
- Increased risk of death in the Bdq arm of the clinical trial*
- Better safety profile of Dlm
- Dlm presents less drug-drug interaction with ART
- There is a potential cross-resistance between Cfz and Bdq
- Bdq and Dlm cannot be used in combination

*Diacon AH, Pym A, TMC207-C208 Study Group. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; 371: 723-32.

Option 1

- **Use delamanid for**
  - Any patient requiring Group 5 drugs and who has been previously exposed to clofazimine for more than 2 months
  - Patients susceptible to FQ but for whom the construction of a regimen with four likely effective drugs including an injectable is not possible
  - Other patients who have high risk of unfavorable outcome
    - Patients with extensive lesions
    - Patients with increased likelihood of treatment failure, or death
    - Patients coming from catchment areas that have poor MDR-TB treatment outcomes despite good programmatic conditions
- **Use bedaquiline for**
  - Patients with resistance to FQ (including XDR-TB)
  - Contact with a patient with resistance to FQ
  - Patients who are "failure" of an MDR-TB regimen per 2013 definitions

Option 2

Use delamanid first in all eligible patients for a new TB drug,
(given the safety profile, shorter half-life and lower drug-drug interaction)

For patients that fail a regimen with delamanid, design the new regimen with bedaquiline.

Because of more experience with bedaquiline and excellent results published in FQ resistance and XDR-TB*, favor Option 1.

* Guglielmetti L, et al; Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis* 2015; 60(2): 188-94.

Monitoring of patient under Delamanid

Baseline

- ECG (QTcF)
- Albuminemia
- Electrolytes (K+, Ca++, Mg+)

Follow-up

- ECG at least 2, 4, 8, 12 and 24
- ECG monthly if taking other QT prolonging drugs or strong CYPA4 inhibitors
- Electrolytes (K+; Ca++, Mg+) monthly

Monitoring for other drugs in the regimen
Bacteriological monitoring
Detection and management of adverse events
Pharmacovigilance

Conclusion

- Delamanid is a new drug in the desperately weak armament against MDR-TB
- Available data show a good safety profile and potentially large indications
- Should be used with
  - Proper patient inclusion criteria
  - Adherence to the key principles of designing a MDR-TB regimen
  - Adequate monitoring and management of adverse drug reactions
  - Good pharmacovigilance

Additional chance of improved outcomes for MDR-TB

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