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

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Cohort event monitoring in the Republic of Belarus

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National aDSM projects: epidemiological necessity

MDR-TB

- Previously treated
- New

2015; 66

Treatment initiation in 2013

XDR-TB treatment results

- 38
- 33
- 17
- 7

Adherence and tolerability raising through implementation of intensive monitoring and risk minimisation measures

Introduction of new components and regimens of TB treatment

Ensuring adequate laboratory and clinical monitoring

Ensuring immediate measures

Ensuring standardised safety and efficacy data collection, MMP

Introduction of active pharmacovigilance
Goals and objectives of active drug safety monitoring

Goals:
- reduce risks for MDR-TB patients associated with second-line drugs
- develop structured and standardized data to formulate policies for new TB drugs use

I. Exposure to treatment when benefits outweigh risks:
- provide control at drug administration stage (inclusion/exclusion criteria)
- ensure systemic clinical and laboratory evaluation on safety parameters
- take immediate measures if adverse effects found

II. Develop structured and standardized data on safety and efficiency profiles of new TB drugs:
- collect, record and evaluate data on safety and efficiency parameters
- data on profile modifying risk factors
- data on efficiency of measures aimed at ADR monitoring/prevention/management
Active drug safety monitoring programmes in the Republic of Belarus

2014

Cohort monitoring of Lzd safety and efficacy as a part of combination TB treatment

- 256 patients
- Lzd treatment < 1 year
- Lzd treatment > 1 year (up to 2 years)

2015

Cohort monitoring of Bdq safety and efficacy as a part of combination TB treatment

- 184 patients
- Bdq treatment 6 to 9 months
- 14 patients under 18 years old
- 1 patient – exposure during pregnancy

2016 год

Cohort monitoring of Dlm safety and efficacy as a part of combination TB treatment

- 11 patients
Inclusion, monitoring and risk minimisation

During whole course of treatment:
- Regular ECG monitoring, QTcF evaluation
- Regular laboratory monitoring of AST, ALT, AP, bilirubin, GGT, lipase, creatinine, GFR, TSH, K+, Mg2+, blood parameters, glucose
- Regular clinical monitoring, audiogram, ophthalmological exam, neurological exam

At baseline:
- QT interval ≤ 400 msec
- AST, ALT < 3 x ULN, bilirubin – < 1.5 x ULN
- No history of cardiac arrhythmia (torsade de pointes, ventricular arrhythmias), coronary artery disease

Treatment discontinuation:
- QT prolongation > 500 мсек
- Increase in AST, ALT > 5 x ULN, or AST, ALT, bilirubin > 2 x ULN

Drug interactions monitoring:
- With TB drugs causing QT prolongation (fluoroquinolones, clofazimine)
- With hepatotoxic drugs
- CYP3A4 inhibitors (ARV, ketoconazole) and inductors
Instruments of cohort monitoring

Data collection forms:
- Treatment initiation form
- Treatment evaluation form

About 3400 data collection forms included in DB
Interim data on efficacy and safety of new drugs

Interim safety data

**Up to 100% of patients develop AE**
(mild and medium severity; SAE – up to 5%)

**Serious AE**

- **Cardiovascular disorders**
  (↑ QT, arrhythmias, cardiac failure)

- **Hepatobiliary disorders**
  (toxic hepatitis)

- **Renal and urinary tracts disorders**
  (toxic nephropathy)

- **Plasma electrolytes disturbances**
  (hypokalaemia, hypomagnesaemia)

3 fatal outcomes

- **1 patient – Bdq treatment phase (2 weeks)**,
  Stage 4 HIV infection, CNS lymphoma
  (causal relationship unlikely)

- **1 patient – Bdq treatment phase**
  Acute pulmonary and cardiac failure
  (causal relationship possible)

- **1 patient – continuation phase**
  Mesenteric vein trombosis
  (causal relationship unlikely)
Interim data on efficacy and safety of new drugs (2)

Most common AE

- **Metabolic disturbances in up to 74%** (hyperuricaemia)
- **Hepatobiliary disorders 70%**
  - (↑ ALT, AST, AP, bilirubin, toxic hepatitis)
- **Disturbances of plasma electrolyte concentrations up to 51%**
  - (↓ Mg$^{2+}$, K$^{+}$ levels)
- **Cardiovascular disturbances up to 43,6%**
  - (↑ QT, arrhythmias, ECG abnormalities, non-specific myocardial abnormalities)
- **Gastrointestinal disorders up to 24%**
  - (nausea, heartburn, vomiting, abdominal pain)
- **Renal and urinary tracts disorders up to 23%**
  - (↑ creatinine, ↑ GFR, toxic nephropathy)
- **CNS abnormalities up to 21,7%**
  - (headache, paresthaesia, dizziness)
- **Psychiatric disorders up to 17,4%**
  - (insomnia, agitated state, depression, suicidal ideation)
Practical outcomes of PV implementation

- **Drug administration control**: include patients with a favourable benefit-risk ratio
- **Condition control**: thorough monitoring of drug efficiency and safety parameters throughout therapy to determine deviations and take response measures
  - **Provide personal approach** in evaluation of risk factors
  - **Improve safety, adherence** and therapy results
- **Control drug administration**, avoid inadequate administration and monitoring; and decrease drug resistance risks
  - **Collect structured and standardized data** on efficiency and safety profiles of new TB drugs, including their use as part of various ATT regimes and co-morbidities management – **amend currently available data**
  - **Collect qualitative data on risk parameters** (severity, risk factors, profile modifying factors, probability, prevention possibility, and monitoring and correction efficiency) – **amend currently available data**
- **Develop expertise** in monitoring and drug safety
- **Ensure implementation** of safety control and reporting and raise vigilance
- **Implement PV in NTP**
THANK YOU FOR YOUR ATTENTION!