OPERATIONAL RESEARCH

Prevalence and determinants associated with treatment outcomes in M/XDR pulmonary TB with Bedaquiline containing regimens (2013 – 2016).

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Всемирная организация здравоохранения
Европейское региональное бюро

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Aim and Objectives:

Using countrywide TB treatment data of Belarus from 2013 to 2016, this study aims to:

1. Determine time to sputum conversion, and treatment outcomes among adult patients with M/XDR PTB treated with Bdq compared to those with standard treatment regimens;
2. Describe adverse events among patients treated with Bedaquiline.

Specific objectives:

1) to compare time of sputum conversion (by smear and by culture) and treatment outcomes among M/XDR PTB patients treated with Bdq compared to those treated with standard treatment regimens.
2) to determine variables associated with different treatment outcomes in M/XDR PTB patients in the above cohorts.
3) To describe the frequency, type and severity of adverse events in M/XDR PTB patients treated with Bdq.

Methods

- This was a nationwide, retrospective cohort study of all adult ((≥18 years) M/XDR-TB patients in Belarus who have been enrolled in treatment from 2013 to 2016.

- All M/XDR PTB patients treated anywhere in Belarus with standard treatment regimens (2013-2014) were included in the ‘standard treatment’ cohort.

- The bedaquiline cohort (2015-2016) included all patients treated with bedaquiline in Belarus during these years. Bedaquiline was given for 6 months as part of the intensive treatment phase.

Data variables

- Data variables collected from the national Belarus TB register.

- For both cohorts included:
  - ✓ patient demographics,
  - ✓ treatment regimen,
  - ✓ place of residence (urban/rural),
  - ✓ HIV status,
  - ✓ baseline DST,
  - ✓ baseline sputum smear status,
  - ✓ treatment outcomes,
  - ✓ treatment start date,
  - ✓ monthly smear and culture results during the first six months of therapy (with corresponding dates),
  - ✓ end of treatment smear and culture results.
  - ✓ type, severity and seriousness of adverse events were also collected for patients treated with Bedaquiline, from a specific registry for pharmacovigilance of new TB drugs in Belarus.

Statistical analysis

- Data were analyzed using R version 3.5.2, the “EasyStat” online statistical platform(14) and Stata version 15.0 (College Station, Texas, USA).
- Data were summarized using descriptive statistics.
- Treatment outcomes among patients treated with bedaquiline were compared to those treated with standard regimens using multivariable logistic regression.
- Time to culture conversion during the first six months of treatment was analyzed using a multivariable competing risks regression model.
- Those with missing treatment start dates, and with no available culture results during treatment were excluded. Levels of significance were set at 5%.

Ethics

- Local ethics approval was obtained from the Local Ethical Committee of the Republic Scientific and Practical Centre of Pulmonology and Tuberculosis.
- Ethics exemption was also received from the WHO Research Ethics Review Committee.
- As this was a retrospective analysis of routinely collected programmatic data and the non-disclosure of individual patients information was guaranteed, patient informed consent waiver was granted.

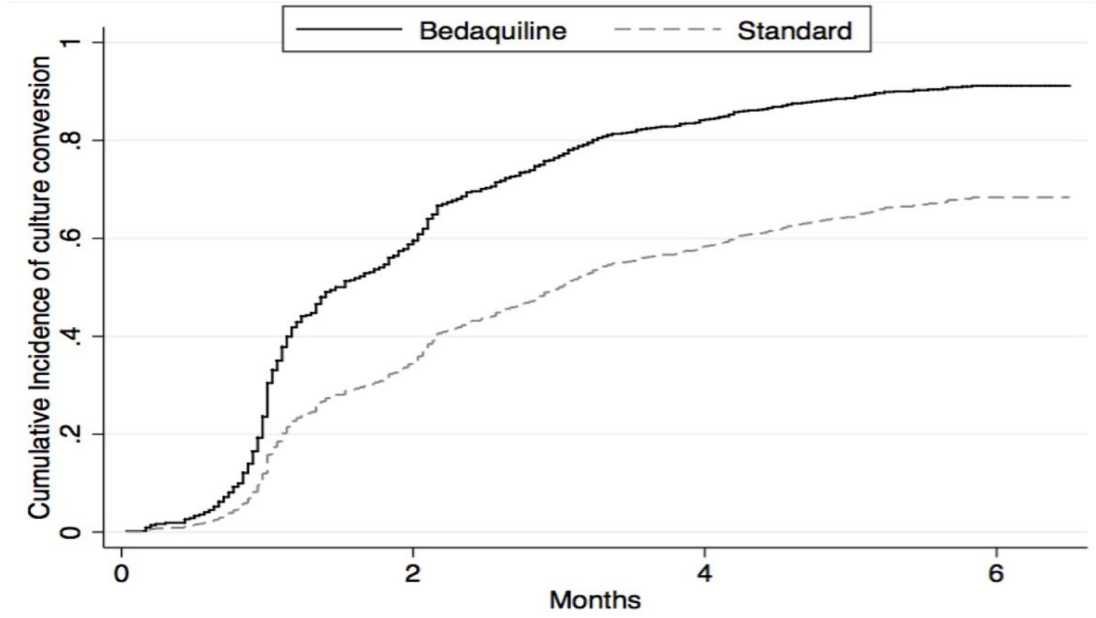
Table 1: Baseline characteristics of the study cohort of MDR and XDR-TB patients in Belarus (2013-2016), stratified by treatment regimen. Data shown as n(%) or mean(+/-SD), where indicated.

		Bedaquiline (n=179)	Standard treatment (n=746)	Total (n=925)
Age	(mean +/- SD)	39.83 (+/- 11.65)	44.21 (+/- 12.84)	43.36 (+/- 12.73)
Gender	Female	51 (28.5%)	151 (20.2%)	202 (21.8%)
	Male	128 (71.5%)	595 (79.8%)	723 (78.2%)
Residence	Rural	68 (38%)	66 (8.8%)	134 (14.5%)
	Urban	107 (59.8%)	641 (85.9%)	748 (80.9%)
	Missing	4 (2.2%)	39 (5.2%)	43 (4.6%)
HIV status	Negative	175 (97.8%)	648 (86.9%)	823 (89%)
	Positive	4 (2.2%)	44 (5.9%)	48 (5.2%)
	Missing	0 (0%)	54 (7.2%)	54 (5.8%)
Sputum smear	Negative	53 (29.6%)	210 (28.2%)	263 (28.4%)
	Positive	126 (70.4%)	534 (71.6%)	660 (71.4%)
	Missing	0 (0%)	2 (0.3%)	2 (0.2%)
DST	MDR	42 (23.5%)	566 (75.9%)	608 (65.7%)
	XDR	137 (76.5%)	167 (22.4%)	304 (32.9%)
	Missing	0 (0%)	13 (1.7%)	13 (1.4%)

Table 2: Final treatment outcomes for MDR- and XDR-TB patients in Belarus (2013-2016), stratified by treatment regimen.

	Bedaquiline (n=179)	Standard treatment (n=746)	Total (n=925)
Favourable			
- Cured	145 (81%)	339 (45.4%)	484 (52.3%)
- Treatment completed	20 (11.2%)	89 (11.9%)	109 (11.8%)
Unfavourable			
- Died	4 (2.2%)	93 (12.5%)	97 (10.5%)
- Failure	3 (1.7%)	116 (15.5%)	119 (12.9%)
- Lost to follow-up	7 (3.9%)	105 (14.1%)	112 (12.1%)
- Not recorded	0 (0%)	4 (0.5%)	4 (0.4%)

Figure 1: Cumulative incidence of culture conversion among MDR- and XDR-TB patients in Belarus (2013-2016), using competing risks regression model



Months	0 to 1	1 to 2	2 to 3	3 to 4	4 to 5	5 to 6
Standard treatment						
N	155	111	83	49	27	14
Conversions	44	28	34	18	11	4
Lost / died	0	0	0	4	2	6
Bedaquiline						
At risk	577	504	320	216	164	120
Conversions	70	156	74	42	31	17
Lost / died	3	28	30	10	13	53

Table 5: Category, severity and seriousness of adverse events among MDR- and XDR-TB patients treated with Bedaquiline in Belarus (2015-2016)

	All	Severity			Seriousness	
		Mild	Moderate	Severe	Not serious	Serious
Any adverse event	151 (84.4)					
Nervous system	14 (7.8)	6 (42.3)	4 (28.6)	3 (21.4)	11 (78.6)	3 (21.4)
Cardiac	89 (49.7)	56 (62.9)	5 (5.6)	18 (20.2)	79 (88.8)	10 (11.2)
Gastrointestinal	28 (15.6)	21 (75)	3 (10.7)	0 (0)	28 (100)	0 (0)
Hepatobiliary	132 (73.7)	98 (74.2)	23 (17,4)	10 (7.6)	128 (97.0)	4 (3.0)
Musculoskeletal	9 (5)	7 (77.8)	1 (11.1)	0 (0)	9 (100)	0 (0)
Other	6 (3,4)	0 (0)	0 (0)	6 (100)	0 (0)	6 (100)

Discussion

- We found that bedaquiline-containing regimens were highly effective, in comparison to previous regimens, with better treatment outcomes, and faster culture conversion.

- Bedaquiline appeared safe. Serious adverse events were detected only in 23 cases among 179 patients. But all patients in the cohort completed six months of therapy.

- Strengths of this study including the large sample size, making this the largest study to our knowledge to evaluate safety and efficacy of bedaquiline in Eastern Europe.

- A limitation of the current study is that, in addition to bedaquiline, other effective drugs (such as fluoroquinolones and linezolid) may have been used with differing frequency in treatment regimens between the periods of our ‘standard treatment’ (2013-2014) and bedaquiline (2015-2016) cohorts.

- In summary, our data demonstrate that bedaquiline-containing regimens are safe and highly effective for patients with highly-resistant TB in Belarus, with excellent treatment outcomes and faster time to culture conversion compared to previous regimens.

Thank you