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Bedaquiline *versus* injectable containing regimens for rifampicin-resistant and multidrug-resistant tuberculosis in a reference center in Brazil – a real-world evidence study using a retrospective design

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Abstract

Background Drug resistance (DR) is one of the several challenges to global tuberculosis (TB) control. The implementation of bedaquiline (BED) for DR-TB after more than 40 years was expected to improve treatment outcomes as well as microbiologic conversion and adverse events (AE) occurrence.

Methods Retrospective cohort study based on secondary data of patients with rifampicin-resistant (RR) or multidrug-resistant (MDR) TB reported to the Outpatient Clinic of Mycobacterial Diseases of the Thorax Diseases Institute – Federal University of Rio de Janeiro - Brazil, between 2016 and 2023. We aimed to evaluate microbiologic conversion, AE and TB treatment outcomes and compare them according to the treatment regimen used for RR/MDR-TB patients under routine conditions [Injectable Containing Regimens (ICR) *versus* BED Containing Regimens (BCR)]. Logistic regression and survival analysis using Cox regression and Kaplan Meier curve were used for statistical analysis.

Results Of the 463 DR-TB patients notified during the study period, 297 (64.1%) were included for analysis (ICR = 197 and BCR = 100). Overall AEs were more frequent (83.7 vs. 16.3%, $p < 0.001$) and occurred earlier in the ICR group (15 days vs. 65 days, $p = 0.003$). There were no cases of cardiotoxicity requiring interruption of BED treatment. None of the regimens of treatment tested were associated with smear or culture conversion on Cox regression analysis ($p = 0.60$ and 0.88, respectively). BED-containing regimens were also associated with favorable outcomes in multivariable logistic regression [adjusted odds ratio (aOR) = 2.63, 95% confidence interval (CI)1.36–5.07, $p = 0.004$], as higher years of schooling, primary drug resistance, and no previous TB treatment. In the survival analysis, BCR was inversely associated with the occurrence of AE during treatment follow-up (aHR 0.24, 95% CI 0.14–0.41, $p < 0.001$). In addition,

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TB treatment regimens with BED were also associated with favorable outcomes (aHR 2.41, 95% CI 1.62–3.57, $p < 0.001$), along with no illicit drug use and primary drug resistance.

Conclusions The implementation of a fully oral treatment for RR/MDR-TB in a reference center in Brazil was safe and associated with favorable outcomes under routine conditions, despite social, demographic, and behavioral factors that may influence TB treatment completion.

Keywords Tuberculosis, Bedaquiline, Adverse events, Microbiological conversion, Treatment outcome

Introduction

Tuberculosis (TB) affects more than 10 million people worldwide each year, yet it is preventable and mostly curable. Despite the effective treatment of latent and active TB, we are still far from achieving the goals of the End TB Strategy [1].

Drug resistance is one of many challenges that must be overcome before the alarming number of TB cases can be reduced. According to WHO, the estimated proportion of people with TB who had multidrug-resistant (MDR) or rifampicin-resistant (RR) TB was 3.3% among new cases and 17% among those previously treated cases in 2022 [2].

Bedaquiline (BED) was the first new clinically approved TB drug developed in more than 40 years and quickly became the *core* of regimens for RR/MDR-TB in combination with linezolid (LNZ), levofloxacin (LFX), terizidone (TRZ) and clofazimine (CFZ) [3].

In 2014, a phase IIb clinical trial demonstrated the efficacy and safety of BED, with a significant improvement in treatment outcomes [4]. The drug was then used under a compassionate use agreement by several national TB programs until it was recommended by the WHO in 2016 and implemented globally for drug-resistant TB (DR-TB) [3].

One of the main concerns with BED-Containing Regimens (BCR) was cardiovascular safety because of the potential for QT interval prolongation on electrocardiogram, leading to arrhythmias [5].

Several scientific publications have evaluated drug-resistant TB regimens containing bedaquiline [4–6]. From observational studies to randomized clinical trials, all of them contributed to the current WHO recommendations [7–10].

Since 2021, the Brazilian Ministry of Health implemented the new regimen for RR/MDR-TB with bedaquiline in combination with LNZ, LFX and TRZ (BCR), in substitution of amikacin (Am) (and previously capreomycin) in combination with LFX, TRZ, ethambutol and pyrazinamide [Injectable Containing Regimens (ICR)]. Although both regimens share the same long duration of 18 months, the former is a totally oral regimen, while the latter includes 8 months of a parenteral drug [11].

We aimed to evaluate microbiologic conversion, adverse events (AE) and TB treatment outcomes before and after the implementation of BCR in RR/MDR-TB patients under routine conditions at the Newthon Bethlem Outpatients Clinic of the Thorax Diseases Institute – Federal University of Rio de Janeiro, Rio de Janeiro, the city with the highest incidence of drug-resistant TB in Brazil.

Methods

A real-world evidence study with a retrospective cohort design was conducted based on secondary data extracted from the database of the *Sistema de Tratamentos Especiais - TB* (SITE-TB), where patients with DR-TB reported between 2016 and 2023 were registered (Ethics Committee approval # 5.959.943).

SITE-TB is a Brazilian Internet platform implemented in 2013 in all Brazilian states, with the aim of routinely monitoring all persons with drug-resistant tuberculosis in Brazil, as well as qualifying tuberculosis drug control [12]. The online website also allows physicians to report drug-resistant TB cases in the country and to register patients` follow-up, including microbiological curve, radiological evolution and AE occurrence. All drug changes during TB treatment need to be registered in the platform, making it an effective way to manage and supply TB drugs for the different national reference centers for DR-TB.

All patients with RR/MDR-TB reported and treated at our clinic during the study period were eligible. To be included, TB treatment regimens must have included amikacin or capreomycin, used in Brazil until 2021 (ICR), or bedaquiline (BCR) according to the recommendations of the Brazilian Ministry of Health [11]. Patients with a change of diagnosis and those transferred to another health center were excluded. Patients who were later found to be rifampicin-monoresistant based on phenotypic drug susceptibility testing were still included in the analysis if the treatment regimen using injectable drugs or bedaquiline was maintained.

Favorable outcomes of TB treatment were considered to be cure, completion of treatment [13] and patients who were still on treatment but had completed at least 6 months of treatment with good adherence. Unfavorable outcomes included loss to follow-up, failure, resistance evolution, death [13] or change of regimen due to AEs. Adverse event data were collected as described in the

SITE-TB database during the patient follow-up visits to the outpatient clinic. Times to smear and culture conversion were calculated based on the first day of treatment and the day the next negative biologic specimen was obtained.

Descriptive analysis was performed through estimates of median and interquartile range (IQR) of the quantitative variables and simple and relative frequencies of the qualitative variables.

For the quantitative variables, the Shapiro-Wilk test was performed to test for normal distribution. For the variables with an abnormal distribution, the Mann-Whitney test was used to compare the medians of two independent variables. The Chi-square test was used to test the association between the qualitative variables.

For the multiple logistic regression analysis, the covariates in the model were selected according to the p-value of the test in the corresponding Chi-square tests, considering values less than 0.2 as possible predictors of the outcome variable in the BCR and ICR groups. The process of selecting the final model was done by the stepwise (backward) method until all variables were considered significant with p-values below 0.05. Variables with statistical significance in the regression analysis were tested for interactions.

The Cox regression model was used to estimate the hazard ratio (HR) for comparing the two TB treatment regimens used (BCR and ICR) over time. Simple models were constructed to estimate HR without adjustment, and then models with all covariates were adjusted to estimate the adjusted hazard ratio (aHR).

Kaplan-Meier curves were constructed with the event of interest, i.e., adverse events, smear and culture conversions or TB treatment outcomes, and the time (in days) until its occurrence. The log-rank test was used to compare two or more curves.

The significance level used was 5%, and all analyses were performed in the R 4.1.0 environment (R Core Team, 2021).

Results

During the study period, 463 patients were diagnosed with drug-resistant TB and 166 were excluded from the analysis (151 had other drug-resistance patterns, 9 were treated with other regimens, 6 had a change of diagnosis or were transferred).

The study population was predominantly men (63%), aged between 26 and 50 years (56%), non-white (68%), and with a low level of education (<7 years) (53%). Regarding social habits associated with TB risk, 25% had a history of alcoholism, 30% were smokers and 28% reported illicit drug use. 75% had MDR-TB, 26% had a previous history of any DR-TB and 48% had primary resistant TB. Demographic and clinical data and social habits characteristics of the 297 patients included for analysis are summarized in Table 1, according to TB treatment groups. There was no statistically significant difference in demographic and clinical characteristics between them.

Although overall AEs were more frequent (83.7 vs. 16.3%, $p<0.001$) and occurred earlier in the ICR group (15 days vs. 65 days, $p=0.003$), we did not observe a statistically significant difference in the presentation of AE requiring treatment interruption between the groups of interest (Table 2).

White ethnicity, higher years of education (>7 years), not smoking and not using illicit drugs were associated with favorable TB treatment outcomes in the bivariate regression analysis, along with primary (vs. acquired drug resistance) and having (vs. not having) previous DR-TB. MDR-TB was inversely associated with favorable outcomes when compared with RR-TB or rifampicin-monoresistant TB (Table 3).

In multivariate logistic regression, when adjusted for ethnicity, years of education, comorbidities (diabetes mellitus, corticosteroid and immunobiologic use), alcoholism, smoking, illicit drug use, TB presentation, type of drug resistance, drug resistance pattern, previous DR-TB treatment, treatment regimen and AE (included in the model because they had a level of significance<0.20), only higher years of education (>7 years), primary (vs. acquired drug resistance), no history of previous DR-TB treatment and BCR persisted in the final model and were associated with favorable outcomes (Table 3). The absence of AE was inversely associated with favorable outcomes, even after adjustment for possible confounders (Table 3).

Survival analysis of time until microbiologic conversion in days showed that smoking was inversely associated with smear conversion. On the other hand, primary resistance showed a positive association with microbiologic conversion when compared with those with acquired resistance (Table 4). None of the TB treatment regimens were associated to smear or culture conversion (Fig. 1).

Age groups above 26 years showed a higher risk ratio for AE occurrence over time, but previously treated DR-TB was inversely associated with it when compared to those who had never had DR-TB (Table 4).

Bedaquiline-containing regimens were inversely associated with the occurrence of AE in Cox regression analysis (aHR 0.24, 95% CI 0.14–0.41, $p<0.001$). TB treatment with BCR was also associated with favorable outcomes (aHR 2.41, 95% CI 1.62–3.57, $p<0.001$), as were no illicit drug use and primary drug resistance, even after adjustment for potential confounders (Table 4). Kaplan-Meier's curves shown in Fig. 1 register significant associations of BCR with time in days to AE occurrence and to treatment outcome ($p<0.0001$ for both variables), while

Table 1 General characteristics of the study population according to the regimen of treatment used (*N* = 297)

		Regimen of treatment				
		Injectable Containing Regimens (*N* = 197)		Bedaquiline Containing Regimens (*N* = 100)		
Variable		**N**	**%**	**N**	**%**	***p-value****
Sex	Male	124	62.9	64	64.0	0. 96
	Female	73	37.1	36	36.0	
Age (Years)	< 26	49	24.9	19	19.0	0. 52
	26–50	108	54.8	59	59.0	
	> 50	40	20.3	22	22.0	
Ethnicity (*N* = 292)	Non – White	129	66.1	74	76.3	0. 10
	White	66	33.8	23	23.7	
Years of education (*N* = 263)	≤ 7	109	58.3	48	63.1	0. 55
	> 7	78	41.7	28	36.9	
Comorbidities						
	Diabetes Mellitus	10	5.1	12	12.0	0. 05
	Mental illness	8	4.1	3	3.0	0. 89
	Hepatitis	3	1.5	1	1.0	1. 00
	Renal failure	1	0.5	2	2.0	0. 55
	Cancer	5	2.5	1	1.0	0. 65
	Use of CTC	5	2.5	0	0	0. 26
	Use of immunobiologics	2	1.0	2	2.0	0. 87
HIV	Negative	118	59.9	60	60.0	0. 21
	Unknown	53	26.9	33	33.0	
	Positive	26	13.2	7	7.0	
Social habits						
	Alcoholism	45	22.8	30	30.0	0. 23
	Smoking	56	28.4	33	33.0	0. 50
	Drug Use	50	25.4	34	34.0	0. 15
TB presentation	Disseminate	9	4.6	6	6.0	0. 84
	Extrapulmonary	5	2.5	2	2.0	
	Pulmonary	183	92.9	92	92.0	
Resistance Pattern	Other R resistance	42	21.3	32	32.0	0. 06
	MDR	155	78.7	68	68.0	
Type of Resistance	Acquired	102	51.8	50	50.0	0. 87
	Primary	95	48.2	50	50.0	
Previous DR-TB	No	140	71.1	81	81.0	0. 09
	Yes	57	28.9	19	19.0	
Treatment Outcomes	Cure	61	31.0	19	19.0	< 0.001
	Completed Treatment	43	21.8	15	15.0	
	On treatment (≥ 6 m)	4	2.0	27	27.0	
	Lost to follow up	62	31.5	27	27.0	
	Death	13	6.6	5	5.0	
	Failure	10	5.1	6	6.0	
	Resistance Evolution	4	2.0	1	1.0	
Outcome Categories	Unfavorable	93	47.2	39	39.0	0.17
	Favorable	104	52.8	61	61.0	

*Chi-square test

Legend: N = Number of observations; %= relative frequency; CI = Confidence interval; CTC = Corticosteroids; HIV = Human Immunodeficiency virus; TB = Tuberculosis; R = Rifampicin; MR = Multidrug; DR-TB = Drug Resistant Tuberculosis

Table 2 Adverse events according to regimen of treatment

	Treatment Regimen				
	Injectable Containing Regimen		Bedaquiline Containing Regimen		
Adverse Event	**N**	**%**	**N**	**%**	***p-value****
Overall AE	108	83. 7	21	16. 3	< 0.001
Time in days until first AE, days (IQR)		15 (31.7)		65 (93)	0.003
Hepatitis	3	100. 0	0	0. 0	1. 00
Peripheral neuropathy	7	70. 0	3	30. 0	0. 44
Optic neuropathy	6	60. 0	4	40. 0	0. 09
Arthralgia	65	84. 4	12	15. 6	0. 97
Nephrotoxicity	5	100. 0	0	0. 0	0. 70
Ototoxicity	7	100. 0	0	0. 0	0. 50
Rash	13	100. 0	0	0. 0	0. 20
Psychiatric symptoms	14	100. 0	0	0. 0	0. 17
Hypothyroidism	3	100. 0	0	0. 0	1. 00
Myelotoxicity	1	50. 0	1	50. 0	0. 74

*Chi-square test

Legend: N = absolute frequency; %= Relative frequency; AE = Adverse event; IQR = Interquartile range

microbiologic conversion did not show statistically significant differences between TB treatment groups.

Discussion

In this cohort of patients, followed at a reference center in Rio de Janeiro, Brazil, BCR was associated with favorable TB treatment outcomes and a lower risk of AEs, although no benefit was seen in terms of microbiologic conversion.

To our knowledge, this is the first study to analyze bactericidal activity, AE occurrence and TB treatment outcomes after the implementation of bedaquiline for RR/MDR-TB under routine conditions in Brazil. We registered an overall favorable treatment outcome of 55.9%, a level lower than the globally reported 63% by WHO in 2020 [1], the frequency of favorable outcomes was almost 10% higher in our center after the implementation of BCR (61% vs. 52,8%) (Table 1). In addition, the association between bedaquiline regimens and favorable treatment outcomes was demonstrated in multivariate and survival analysis.

A recent meta-analysis including observational cohorts and experimental studies found that the pooled treatment success rate of BCR was 78.4% [14]. This success rate is likely related to the inclusion of patients from

Table 3 Bivariate and multivariate logistic regression analysis of factors associated with favorable tuberculosis treatment outcomes

Variable		**OR**	**95% CI**	***p*-value***	**aOR**	**95% CI**	***p*-value***
Ethnicity (*N* = 292)	Non-White	Ref					
	White	1.91	1.14–3.21	0.01	-	-	-
Education (*N* = 263)	Up to 7 years	Ref					
	More than 7 years	2.59	1.54–4.36	< 0.001	2.31	1.30–4.09	0.004
Diabetes Mellitus	Yes	Ref					
	No	0.45	0.77–1.18	0.10	-	-	-
Alcoholism	Yes	Ref					
	No	1.65	0.97–2.79	0.06	-	-	-
Smoking	Yes	Ref					
	No	1.88	1.14–3.19	0.01	-	-	-
Illicit drugs	Yes	Ref					
	No	1.82	1.09–3.03	0.02	-	-	-
Tuberculosis Presentation	Both	Ref					
	Extrapulmonary	0.33	0.05–2.37	0.26	-	-	-
	Pulmonary	0.30	0.08–1.09	0.06	-	-	-
Resistance Pattern	Other R resistance	Ref					
	MDR	0.48	0.27–0.84	0.01	-	-	-
Type of Resistance	Acquired	Ref					
	Primary	3.07	1.90–4.96	< 0.001	1.90	1.05–3.45	0.03
Previous DR-TB	Yes	Ref					
	No	4.59	2.60–8.10	< 0.001	2.34	1.14–4.79	0.02
Regimen of Treatment	Injectable Containing Regimens	Ref					
	Bedaquiline Containing Regimens	1.46	0.89–2.38	0.13	2.63	1.36–5.07	0.004
Adverse Events	Yes	Ref					
	No	0.30	0.18–0.49	< 0.001	0.33	0.18–0.60	< 0.001

Legend: OR = Odds Ratio; CI = Confidence Interval; aOR = Adjusted Odds Ratio; R = Rifampicin; MR = Multidrug; DR-TB = Drug Resistant Tuberculosis

Table 4 Cox regression analysis of time in days until favorable tuberculosis treatment outcomes, adverse events occurrence and microbiologic conversion

Variable		HR	CI (95%)	*p*-value	aHR	CI (95%)	*p*-value
Favorable outcome							
Illicit drugs	Yes	Ref			Ref		
	No	1.56	1.08–2.27	0.02	2.66	1.35–5.24	0.005
Resistance Pattern	Other R resistance	Ref			Ref		
	MDR	0.53	0.38–0.74	< 0.002	0.53	0.35–0.81	0.003
Type of Resistance	Acquired	Ref			Ref		
	Primary	1.41	1.03–1.93	0.03	1.58	0.63–1.06	0.03
Regimen of Treatment	Injectable Containing Regimens	Ref			Ref		
	Bedaquiline Containing Regimens	2.34	1.68–3.25	< 0.001	2.41	1.62–3.57	< 0.001
Adverse events							
Age	< 26 years	Ref			Ref		
	26–50 years	1.20	0.76–1.88	0.44	1.94	1.15–3.28	0.01
	> 50 years	1.67	1.00–2.79	0.05	2.01	1.03–3.92	0.04
Previous DR-TB	No	Ref			Ref		
	Yes	0.36	0.22–0.61	< 0.001	0.34	0.19–0.62	< 0.001
Regimen of Treatment	Injectable Containing Regimens	Ref			Ref		
	Bedaquiline Containing Regimens	0.26	0.16–0.42	< 0.001	0.24	0.14–0.41	< 0.001
Smear conversion							
Smoking	No	Ref			Ref		
	Yes	0.74	0.52–1.10	0.11	0.57	0.34–0.97	0.04
Resistance Pattern	Other R resistance	Ref			Ref		
	MDR	0.56	0.37–0.85	0.006	0.46	0.27–0.79	0.005
Type of Resistance	Acquired	Ref			Ref		
	Primary	1.41	1.02–1.94	0.04	1.56	1.02–2.37	0.04
Regimen of Treatment	Injectable Containing Regimens	Ref			Ref		
	Bedaquiline Containing Regimens	1.02	0.74–1.42	0.89	0.89	0.57–1.38	0.60
Culture Conversion							
Regimen of Treatment	Injectable Containing Regimens	Ref			Ref		
	Bedaquiline Containing Regimens	1.17	0.85–1.61	0.33	1.03	0.69–1.53	0.88

Legend: HR = Hazard Ratio; CI = Confidence Interval; aHR = Adjusted Hazard Ratio; R = Rifampicin; MR = Multidrug; DRTB = Drug Resistant Tuberculosis

Legend: ICR = Injectable Containing Regimens; BCR = Bedaquiline Containing Regimens

different countries, which may make comparison with our results difficult. In addition, experimental studies, including randomized clinical trials, although being considered the highest level of evidence to establish causal associations in clinical research, are usually conducted under idealized and tightly controlled conditions, which may affect their external validity and can also influence the results of the meta-analysis and comparison with our results.

In a large global cohort, 74.2% of patients treated with BCR had treatment success, 6.5% died, 2.9% failed and 16.5% were lost to follow-up [15]. Their numbers were better than ours (treatment success = 62%, death = 5%, failure = 7% and loss to follow up = 26%), probably because the inclusion of patients from countries with better socioeconomic and quality of life indicators may affect adherence and treatment conclusions.

Social aspects presented in our casuistic deserve attention, such as level of education, alcoholism, smoking and illicit drug use. These characteristics have already been identified as risk factors for TB in general and for adverse treatment outcomes [16–18]. In our study, these variables were statistically associated with a negative impact on treatment outcome and smear conversion. Our data are consistent with the finding that patients without a history of DR-TB are more likely to complete TB treatment [19], i.e., those who have previously discontinued resistant TB treatment may repeat the behavior, with a higher risk of a new discontinuation, failure, resistance development, or even death [20].

Another worrying finding is the percentage of primary drug resistance in our sample of RR/MDR-TB patients (almost 50%), which represents a public health problem and has been highlighted by other authors [21, 22]. Fortunately, these patients tend to have more favorable outcomes, as shown by another study in a Brazilian scenario [19].

Curiously, the absence of AE was inversely associated with favorable outcomes, unlike previous studies that found an association between drug side effects and

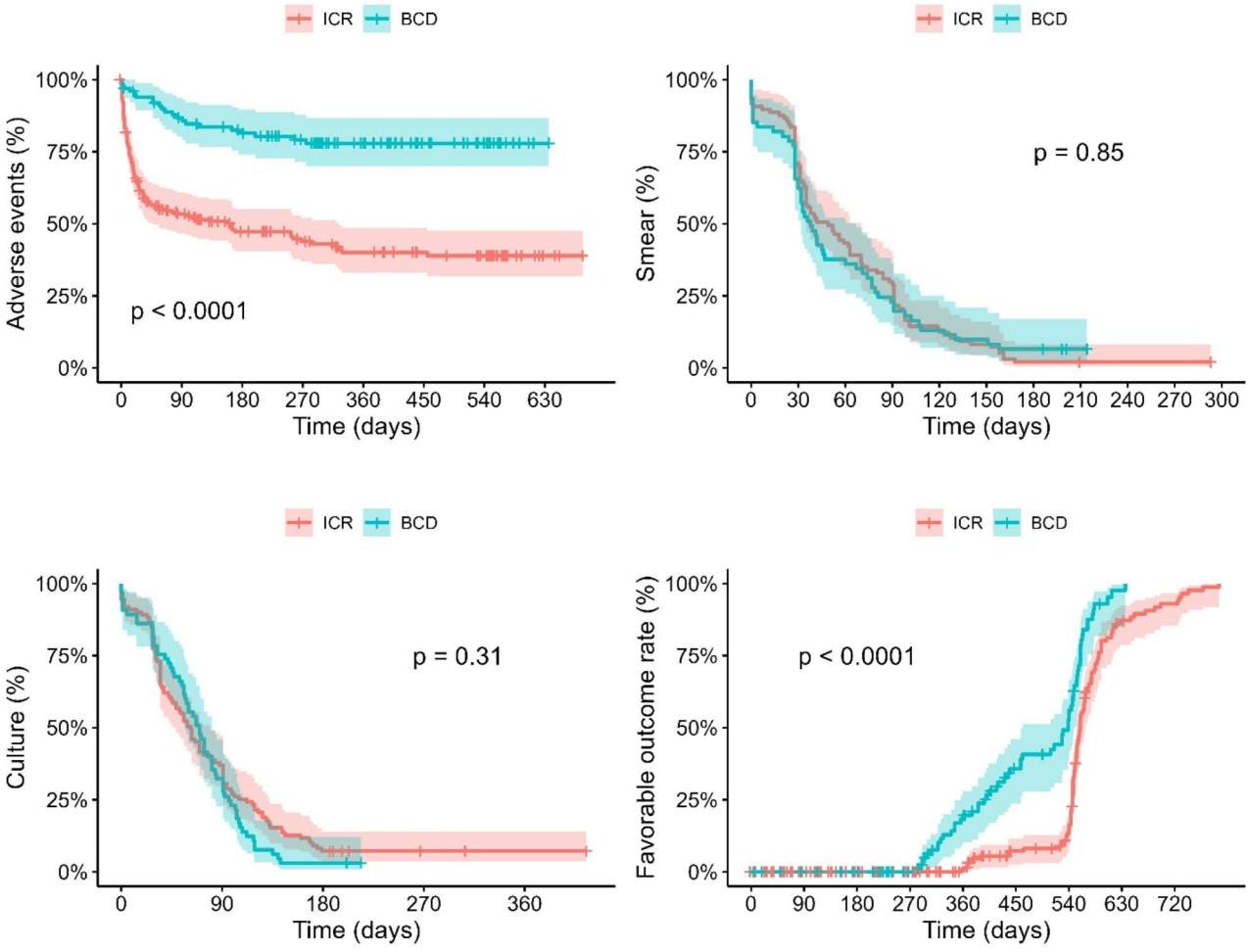

Fig. 1 Kaplan Meier curve of time in days until favorable tuberculosis treatment outcomes, adverse events occurrence and microbiologic conversion

loss to follow-up [23, 24]. We suggest that this could be explained by the fact that only those who continued and completed treatment could complain of AE. On the other hand, patients with unfavorable outcomes, with a poor adherence to medical appointments, did not complain about them.

In addition, the time to first presentation of AE was longer in the BCR group compared the ICR group. In the meta-analysis by Hatami et al. [25], the most common AE potentially attributable to bedaquiline regimens were gastrointestinal symptoms (15.3%), peripheral neuropathy (13.8%), and hematologic disorders (13.6%). In our cohort, the most common serious adverse events in the BCR group were arthralgia, optic neuropathy, peripheral neuropathy and myelotoxicity, but no nephrotoxicity or ototoxicity occurred in the ICR group.

Since the first clinical trials with bedaquiline [4], prolongation of the QT interval on the electrocardiogram has been a concern, but later, studies conducted under routine conditions have not reproduced this finding, mainly because cardiac monitoring is not reported systematically and in sufficient detail to allow for easy comparisons [26]. While some studies show an increased risk of cardiotoxicity [24], none of our patients showed QT interval prolongation, results similar to those published by Chesov et al. [27].

Our study did not have sufficient power to show statistically significant differences in time to smear or culture conversion between TB treatment regimens, as did Charan [28]. However, more recent studies have found an association of higher sputum culture conversion rates with BCR [29–31].

Our main limitation, besides those inherent to retrospective studies, was the impossibility of attributing neither TB treatment outcomes nor AE occurrence specifically to bedaquiline, as treatment regimens include several drugs, but this is a problem common to all similar studies. In addition, although we wanted to contribute

to the research gap in reliable scientific data on AEs, our routine registries were not conducted in a standardized or structured way, as details were not recorded in the medical records or in the instrument used as a source document, making it difficult for us to assess and grade them. Finally, not all patients presented microbiological results at follow-up because they could not produce spontaneous or induced sputum, which could justify our lack of power for this analysis.

Conclusion

In this study, we demonstrated that the implementation of a fully oral bedaquiline-based regimen was safe and associated with a favorable outcome under routine conditions, despite social, demographic, and behavioral factors that may influence TB treatment completion.

Despite rapid changes regarding in RR/MDR-TB treatment in recent years, including the recommendation of the bedaquiline-pretomanide-linezolid (BPaL) regimens [32], real-world evidence studies evaluating regimens still recommended in different settings are important to show the behavior of the disease and its treatment in relation to social and clinical variables under routine conditions and at specific points in history.

The results of the present study made it possible to highlight the positive evolution of Brazilian public institutions over the years, and why not say of global health institutions, leading to the adoption of safer and more effective treatments over the years. In addition, we expect that these data can help the health managers to improve TB care by anticipating the identification of patients at higher risk of adverse TB treatment outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09993-8.

Supplementary Material 1

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Author contributions
APS conceived and supervised the study. CBJ and JAML collected data e filled the database. APS and FCQM analyzed all the data. AK provided advice during the design of the study. APS wrote the manuscript, which has been critically reviewed for intellectual content by AK and FCQM. All authors have read and approved the final version of the manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was submitted to Clementino Fraga Filho – UFRJ Ethics Committee and was approved under # 5.959.943. Because of the retrospective design of the study and the total anonymity of patient's identification, the IRB mentioned above waived the need of informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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