



HAL
open science

Bedaquiline and Repurposed Drugs for Fluoroquinolone-Resistant Multidrug-Resistant Tuberculosis: How Much Better Are They?

Mathieu Bastard, Lorenzo Guglielmetti, Helena Huerga, Armen Hayrapetyan,
Naira Khachatryan, Lusine Yegiazaryan, Jamil Faqirzai, Lana Hovhannisyan,
Francis Varaine, Catherine Hewison

► To cite this version:

Mathieu Bastard, Lorenzo Guglielmetti, Helena Huerga, Armen Hayrapetyan, Naira Khachatryan, et al.. Bedaquiline and Repurposed Drugs for Fluoroquinolone-Resistant Multidrug-Resistant Tuberculosis: How Much Better Are They?. *American Journal of Respiratory and Critical Care Medicine*, 2018, 198 (9), pp.1228-1231. 10.1164/rccm.201801-0019LE . hal-03127733

HAL Id: hal-03127733

<https://hal.science/hal-03127733>

Submitted on 22 Dec 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Bedaquiline and repurposed drugs for fluoroquinolone-resistant MDR-TB: how much better are they?

Mathieu Bastard¹, Lorenzo Guglielmetti^{2,3,4}, Helena Huerga¹, Armen Hayrapetyan⁵, Naira Khachatryan⁶, Lusine Yegiazaryan⁵, Jamil Faqirzai⁶, Lana Hovhannisyan⁶, Francis Varaine², Catherine Hewison²

¹Epicentre, Paris, France

²Médecins Sans Frontières, Paris, France

³APHP, Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux (CNR-MyRMA), Bactériologie-Hygiène, Hôpitaux Universitaires Pitié Salpêtrière-Charles Foix, F-75013, Paris, France

⁴Sorbonne Université, Université Pierre et Marie Curie 06, Unité 1135, Team E13 (Bactériologie), CR7 INSERM, Centre d'Immunologie et des Maladies Infectieuses, Paris, France

⁵National Tuberculosis Control Centre (NTBCC) of Armenia, Yerevan, Armenia

⁶Médecins Sans Frontières, Yerevan, Armenia

Corresponding author: Mathieu Bastard, MSc, Epicentre, 8 rue Saint Sabin, 75011 Paris, France, Tel: +41 22 849 8903, Fax: +33 1 40 21 55 00,

Email: mathieu.bastard@geneva.msf.org

Funding: Médecins Sans Frontières provided the funding for this study.

Authors' contributions: Conception and design: MB, LG, HH, CH, FV; Analysis: MB; Interpretation of results: MB, LG, HH, AH, NK, LE, JF, FV, CH. Draft the manuscript for important intellectual content: MB, LG, HH, CH, and FV.

Running Title: Bedaquiline and repurposed drugs improve MDR-TB outcomes

Introduction

Treatment outcomes of conventional multi-drug resistant tuberculosis (MDR-TB) treatment are overall unsatisfactory, particularly for fluoroquinolone-resistant MDR-TB (1). In addition, long-term follow-up studies have shown that patients who have experienced previous treatment failure contribute importantly to ongoing transmission in the community (2). The introduction of new drugs bedaquiline and delamanid has been reported to improve treatment outcomes of MDR/XDR-TB (3, 4). In addition, there is growing evidence that repurposed drugs such as linezolid, clofazimine, and carbapenems with amoxicillin/clavulanate also have a role to play in MDR/XDR-TB treatment (5, 6). However, there are few reports that assess new regimens rather than the addition of a single new or repurposed drug to a regimen (3, 4, 6).

In Armenia, Médecins Sans Frontières (MSF) has supported the National Tuberculosis Program for the treatment of MDR-TB patients since 2005. In 2013, bedaquiline was introduced into clinical practice through a compassionate use (CU) mechanism. At the same time, the repurposed drugs linezolid and imipenem/cilastatin were available for the first time. Clofazimine was already available. The objective of this study was to assess the clinical impact of regimens containing bedaquiline, linezolid and/or imipenem/cilastatin.

Methods

This is a retrospective cohort analysis of patients started MDR-TB treatment in Armenia. Consecutive confirmed MDR-TB fluoroquinolone-resistant patients were included. We compared treatment outcomes of patients who received WHO-recommended MDR-TB regimens with bedaquiline through CU and linezolid with or without imipenem/cilastatin from April 2013 to April 2015 (CU cohort), to those who received WHO-recommended MDR-TB regimens without bedaquiline, linezolid nor imipenem/cilastatin from September 2005 to April 2015 (non-CU cohort).

Treatment regimens were individually tailored to include sufficient effective drugs according to WHO recommendations. Treatment previous to CU for fluoroquinolone resistant patients included kanamycin or capreomycin, a fluoroquinolone even if resistant, prothionamide, PAS, cycloserine and two of the following: clofazimine, clarithromycin, and amoxicillin-clavulanate. Treatment regimens for the CU cohort included the addition of bedaquiline for only 24 weeks according to CU protocol and linezolid and imipenem/cilastatin (given with amoxicillin clavulanate) as needed, supplied by MSF. Delamanid was not available. All patients received a support package, directly observed treatment and were followed-up monthly with bacteriological and laboratory tests. Drug sensibility testing was performed in Borstel Supranational Reference Laboratory until 2010 and then by the quality assured Armenia National Reference Laboratory. Outcomes were assigned as per WHO guidelines (7). Treatment success was defined as cured or treatment completed.

We estimated the average treatment effect (receiving bedaquiline and repurposed drugs) by inverse-probability-weighted regression-adjustment (IPWRA). The treatment model included gender, age, previous use of second line drugs, previous and actual use of clofazimine, and

resistance profile at treatment initiation, and the outcome model included adherence. Sensitivity analysis by excluding lost to follow-up was performed. Analyses were performed using Stata 15 (Stata Corporation, College Station, Texas, USA).

The study was approved by the relevant health authorities in Armenia and fulfilled the exemption criteria set by the MSF Ethics Review Board for a posteriori analyses of routinely collected clinical data.

Results

A total of 140 patients with pulmonary TB were included, 91 in the non-CU cohort and 49 in the CU-cohort. The two cohorts presented similar characteristics at treatment initiation (Table), although in the CU cohort more patients were previously treated with second-line drugs ($p<0.001$), had previously received clofazimine ($p<0.001$), and had XDR-TB ($p=0.058$). The use of clofazimine was more frequent in the CU cohort ($p<0.001$). All patients in the CU cohort received bedaquiline and linezolid, 76.0% received imipenem/cilastatin plus amoxicillin/clavulanate, and 83.7% received clofazimine. The total number of drugs received at initiation was higher in the CU cohort ($p <0001$).

Faster culture conversion was observed in the CU cohort (Figure A, $p<0.001$). Among patients with positive culture at baseline, 6-month culture conversion reached 73.0% (27/37) in the CU cohort and only 35.6% (31/87) in the non-CU cohort ($p<0.001$). The median time to culture conversion was 2.7 months [IQR 1.9–4.9] in the CU cohort and 5.7 months [IQR 2.7–11.4] in the non-CU cohort.

Treatment success was higher in the CU cohort (30/49, 61.2%) compared to the non-CU cohort (20/91, 22.0%), (Table, $p < 0.001$). The CU cohort also showed a lower proportion of unfavorable outcomes (death or treatment failure) (Figure B, $p < 0.001$). The IPWRA analysis showed that patients in the CU cohort had an estimated statistically significant increase in treatment success of 30.2% (95%CI 15.8–44.5%). Exclusion of patients who were lost to follow-up did not change the results (data not shown).

Discussion

This study shows that regimens containing bedaquiline and repurposed drugs have improved treatment success by 30% compared to previously-available conventional regimens for fluoroquinolone-resistant MDR-TB in Armenia. Significant faster and higher probability of conversion was also observed for patients receiving these regimens. The difference in treatment success between the two cohorts is striking, principally due to a lower proportion of treatment failure indicating better treatment efficacy in the CU cohort. Although improved, the outcomes of the CU cohort are still inferior to those reported in high-resource settings: many factors, including treatment support and social conditions, may account for this difference (8, 9). Patients were given all available effective drugs to construct the regimens: the lower total number of effective drugs reported in the non-CU cohort likely reflects the lack of access to some drugs at this time..

This study has several limitations: the retrospective design, the observational nature of the data and the historical comparator. Some of the differences in the baseline characteristics

may have also impacted the results. However, the robust statistical method used support the validity of our findings. [The safety will be described in a separate study.](#)

In conclusion, new and repurposed drugs can make fluoroquinolone-resistant MDR-TB, and potentially XDR-TB, a disease that is curable in the majority of cases. Despite this evidence, only 15.7% of MDR-TB cases likely to benefit from either bedaquiline or delamanid have received them (10) and no data exists for repurposed drugs. An important scale up of access to bedaquiline and repurposed drugs should be a public health priority and more evidence is needed on cost-effective models of care.

Acknowledgments

We acknowledge the the Armenia Medical Team: Hakob Atchemyan, Ohanna Kirakosyan, Arusyak Melikyan, Ofelya Petrosyan, Armine Serobyan, Narine Danielyan, Tsovinar Aydinyan, Nora Saribekyan and Lusine Yegiazaryan.

References

1. Bonnet M, Bastard M, du Cros P, Khamraev A, Kimenye K, Khurkhumal S, Hayrapetyan A, Themba D, Telnov A, Sanchez-Padilla E, Hewison C, Varaine F. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study. *Int J Tuberc Lung Dis* 2016;20:177–186.
2. Shah NS, Auld SC, Brust JCM, Mathema B, Ismail N, Moodley P, Mlisana K, Allana S, Campbell A, Mthiyane T, Morris N, Mpangase P, van der Meulen H, Omar S V., Brown TS, Narechania A, Shaskina E, Kapwata T, Kreiswirth B, Gandhi NR. Transmission of Extensively Drug-Resistant Tuberculosis in South Africa. *N Engl J Med* 2017;376:243–253.
3. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, Leimane V, Andries K, Bakare N, De Marez T, Haxaire-Theeuwes M, Lounis N, Meyvisch P, De Paepe E, van Heeswijk RPG, Dannemann B, TMC207-C208 Study Group. Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline. *N Engl J Med* 2014;371:723–732.
4. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, Cirule A, Leimane V, Kurve A, Levina K, Geiter LJ, Manissero D, Wells CD. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J* 2013;41:1393–1400.
5. Dooley KE, Obuku EA, Durakovic N, Belitsky V, Mitnick C, Nuermberger EL. World health organization group 5 drugs for the treatment of drug-resistant tuberculosis: Unclear efficacy or untapped potential? *J Infect Dis* 2013;doi:10.1093/infdis/jis460.
6. Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, Wu M, Zen L, Sun H, Liu Y, Gu J, Lin F, Wang

- X, Zhang Z. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. *Eur Respir J* 2015;45:161–170.
7. World Health Organization. *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis Title*. 2014. at http://apps.who.int/iris/bitstream/handle/10665/130918/9789241548809_eng.pdf?sequence=1.
 8. Guglielmetti L, Jaspard M, Le Dû D, Lachâtre M, Marigot-Outtandy D, Bernard C, Veziris N, Robert J, Yazdanpanah Y, Caumes E, Fréchet-Jachym M, French MDR-TB Management Group. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. *Eur Respir J* 2017;49:1601799.
 9. Kuksa L, Barkane L, Hittel N, Gupta R. Final treatment outcomes of multidrug- and extensively drug-resistant tuberculosis patients in Latvia receiving delamanid-containing regimens. *Eur Respir J* 2017;50:1701105.
 10. Cox V, Brigden G, Crespo RH, Lessem E, Lynch S, Rich ML, Waning B, Furin J. Global programmatic use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2018;22:407–412.

Table - Patients' characteristics at treatment start and treatment outcomes for non-compassionate use (non-CU) and compassionate use (CU) cohorts.

	non-CU cohort N=91	CU Cohort N=49	p-value
<i>Characteristic</i>			
Male	72 (79.1)	43 (87.8)	0.203
Age, Median [IQR]	45 [32 – 53]	41 [30 – 52]	0.465
BMI, Median [IQR]	20.5 [17.6 – 23.7]	20.2 [17.8 – 23.4]	0.930
Previously treated	47 (51.6)	49 (100)	<0.001
HIV-positive	6/63 (9.5)	1/49 (2.0)	0.110
XDR-TB	28 (30.8)	23 (46.9)	0.058
Cavity in X-ray	85 (93.4)	45 (91.8)	0.731
Extensive disease	87 (95.6)	46 (93.9)	0.655
Prisoners	21 (23.1)	11 (22.5)	0.933
Diabetes	9 (9.9)	5 (10.2)	0.953
Previous use of Cfz	1 (1.1)	13 (26.5)	<0.001
Number of drugs received at treatment start*, Median [IQR]	6 [6 – 7]	7 [7 – 7]	<0.001
Number of drugs that the patients were resistant to Median [IQR]	6 [5 – 7]	7 [5 – 8]	0.300
Treatment with Cfz in	21 (23.1)	41 (83.7)	<0.001

current regimen			
<i>Treatment outcome</i>			
Cured	11 (12.1)	23 (46.9)	
Treatment completed	9 (9.9)	7 (14.3)	
Death	14 (15.4)	5 (10.2)	
Failure	30 (33.0)	5 (10.2)	
Lost to follow-up	27 (29.7)	9 (18.4)	
Treatment success**	20 (22.0)	30 (61.2)	<0.001
Treatment success excluding lost to follow-up	20/64 (31.2)	30/40 (75.0)	<0.001

Note: IQR = interquartile range; BMI = body mass index; Cfz = clofazimine.

* Including effective and non-effective prescribed drugs

** Sum of cured and treatment completed

Figure – Kaplan-Meier estimates of: (a) culture conversion among patients with positive sputum culture at treatment start, and (b) unfavorable outcome (death or treatment failure), for non-compassionate use (non-CU) and compassionate use (CU) cohorts.