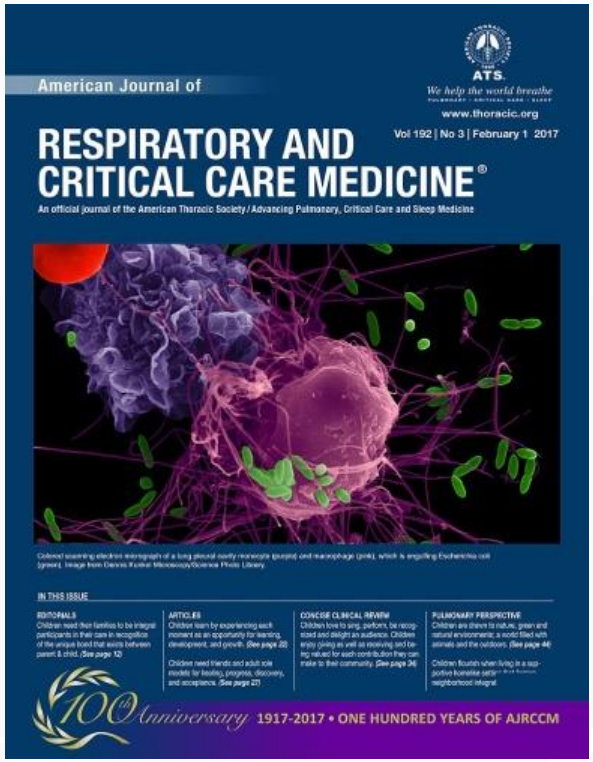
Деламанид – новый противотуберкулёзный препарат. Зарубежные исследования

Culture Conversion in Patients Treated with Bedaquiline and/or Delamanid A Prospective Multicountry Study / M. Franke, P. Khan, C. Hewison // American journal of respiratory and critical care medicine . – 2021. – Vol. 203, N 1. - P. 111 – 119. DOI: 10.1164/rccm.202001-0135OC

Rationale: Bedaquiline and delamanid offer the possibility of more effective and less toxic treatment for multidrug-resistant (MDR) tuberculosis (TB). With this treatment, however, some patients remain at high risk for an unfavorable treatment outcome. The endTB Observational Study is the largest multicountry cohort of patients with rifampin-resistant TB or MDR-TB treated in routine care with delamanid- and/or bedaquiline-containing regimens according to World Health Organization guidance. Objectives: We report the frequency of sputum culture conversion within 6 months of treatment initiation and the risk factors for nonconversion. Methods: We included patients with a positive baseline culture who initiated a first endTB regimen before April 2018. Two consecutive negative cultures collected 15 days or more apart constituted culture conversion. We used generalized mixed models to derive marginal predictions for the probability of culture conversion in key subgroups. Measurements and Main Results: A total of 1,109 patients initiated a multidrug treatment containing bedaquiline (63%), delamanid (27%), or both (10%). Of these, 939 (85%) experienced culture conversion within 6 months. In adjusted analyses, patients with HIV had a lower probability of conversion (0.73; 95% confidence interval [CI], 0.62-0.84) than patients without HIV (0.84; 95% CI, 0.79-0.90; P = 0.03). Patients with both cavitary disease and highly positive sputum smear had a lower probability of conversion (0.68; 95% CI, 0.57-0.79) relative to patients without either (0.89; 95% CI, 0.84-0.95; P = 0.0004). Hepatitis C infection, diabetes mellitus or glucose intolerance, and baseline resistance were not associated with conversion. Conclusions: Frequent sputum conversion in patients with rifampin-resistant TB or MDR-TB who were treated with bedaquiline and/or delamanid underscores the need for urgent expanded access to these drugs. There is a need to optimize treatment for patients with HIV and extensive disease.



Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis in Children: The Role of Bedaquiline and Delamanid / F. Pecora, G. Dal Canto, P. Veronese, S. Esposito // Microorganisms. – 2021. – Vol. 9, N 5. – N 1074. DOI: 10.3390/microorganisms9051074

Multidrug-resistant (MDR) tuberculosis (TB) has been emerging at an alarming rate over the last few years. It has been estimated that about 3% of all pediatric TB is MDR, meaning about 30,000 cases each year. Although most children with MDR-TB can be successfully treated, up to five years ago effective treatment was associated with a high incidence of severe adverse effects and patients with extensively drug-resistant (XDR) TB had limited treatment options and no standard regimen. The main objective of this manuscript is to discuss our present knowledge of the management of MDR- and XDR-TB in children, focusing on the characteristics and available evidence on the use of two promising new drugs: bedaquiline and delamanid. PubMed was used to search for all of the studies published up to November 2020 using key words such as "bedaquiline" and "delamanid" and "children" and "multidrug-resistant tuberculosis" and "extensively drug-resistant tuberculosis". The search was limited to articles published in English and providing evidence-based data. Although data on pediatric population are limited and more studies are needed to confirm the efficacy and safety of bedaquiline and delamanid, their use in children with MDR-TB/XDR-TB appears to have good tolerability and efficacy. However, more evidence on these new anti-TB drugs is needed to better guide their use in children in order to design effective shorter regimens and reduce adverse effects, drug interactions, and therapeutic failure.

microorganisms

MDPI

Review

Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis in Children: The Role of Bedaquiline and Delamanid

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Abstract: Multidrug-resistant (MDR) tuberculosis (TB) has been emerging at an alarming rate over the last few years. It has been estimated that about 3% of all pediatric TB is MDR, meaning about 30,000 cases each year. Although most children with MDR-TB can be successfully treated, up to five years ago effective treatment was associated with a high incidence of severe adverse effects and patients with extensively drug-resistant (XDR) TB had limited treatment options and no standard regimen. The main objective of this manuscript is to discuss our present knowledge of the management of MDR- and XDR-TB in children, focusing on the characteristics and available evidence on the use of two promising new drugs: bedaquiline and delamanid. PubMed was used to search for all of the studies published up to November 2020 using key words such as "bedaquiline" and "delamanid" and "children" and "multidrug-resistant tuberculosis" and "extensively drug-resistant tuberculosis". The search was limited to articles published in English and providing evidence-based data. Although data on pediatric population are limited and more studies are needed to confirm the efficacy and safety of bedaquiline and delamanid, their use in children with MDR-TB/XDR-TB appears to have good tolerability and efficacy. However, more evidence on these new anti-TB drugs is needed to better guide their use in children in order to design effective shorter regimens and reduce adverse effects, drug interactions, and therapeutic failure.

Keywords: multidrug-resistant tuberculosis; extensively drug-resistant tuberculosis; bedaquiline; delamanid; children

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Citation: Pecora, F.; Dal Canto, G.; Veronese, P.; Esposito, S. Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis in Children: The Role of Bedaquiline and Delamanid. *Microorganisms* **2021**, *9*, 1074. https://doi.org/10.3390/microorganisms9051074

Academic Editor: Sarah Fortune

Received: 13 April 2021
Accepted: 10 May 2021
Published: 17 May 2021

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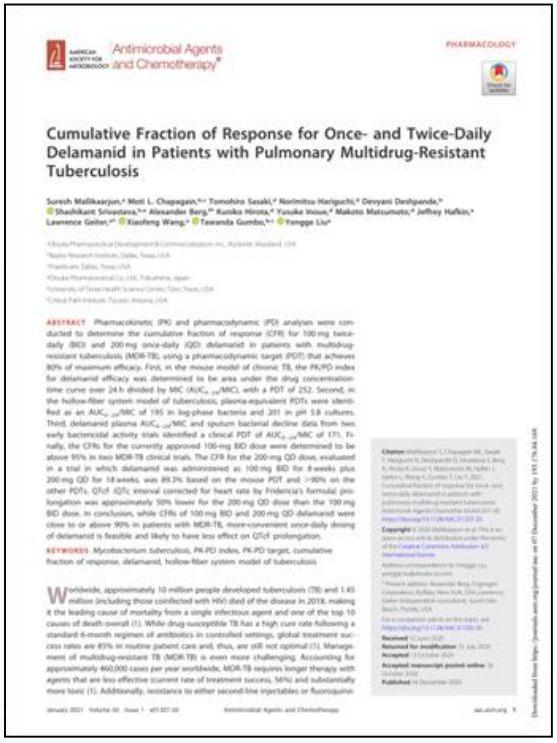
1. Introduction

Tuberculosis (TB) causes even more deaths each year than any other bacterial infection [1]. In 2018, the World Health Organization (WHO) estimated 10.0 million new cases of TB (range 9–11.1 million). The burden of disease is very heterogeneous among countries, with the global average being around 130 new cases per 100,000 population per year. In the same period, TB deaths among HIV-negative people, in 2018, were estimated to be 1.2 million (range 1.1–1.3 million), and 251,000 deaths (range 223,000–281,000) among HIV-infected people. Children (aged <15 years) accounted for 11% of all TB cases in 2018, with higher rates in developing countries [1,2]. Indeed, in Africa, children contribute approximately 30% of incident TB cases. In countries with high HIV prevalence, the peak age prevalence of TB has shifted towards younger adults. These adults are often parents of young children, increasing the exposure of children to TB [3,4].

Multidrug-resistant (MDR) TB has been emerging at an alarming rate over the last few years. Annually, the new cases of MDR and rifampicin-resistant (RR) TB are estimated to be 500,000 [5]. Although an increased number of children is now being diagnosed and treated for TB, a low number is diagnosed for MDR-TB and little data are available on the occurrence of MDR-TB in children [6,7]. It has been estimated that about 3% of

Cumulative Fraction of Response for Once- and Twice-Daily Delamanid in Patients with Pulmonary Multidrug-Resistant Tuberculosis / S. Mallikaarjun, M. Chapagain, T. Sasaki et al. // Antimicrobial agents and chemotherapy. – 2021. – Vol. 65, N 1. – N e01207-20. DOI: 10.1128/AAC.01207-20

Pharmacokinetic (PK) and pharmacodynamic (PD) analyses were conducted to determine the cumulative fraction of response (CFR) for 100 mg twice-daily (BID) and 200 mg once-daily (QD) delamanid in patients with multidrug-resistant tuberculosis (MDR-TB), using a pharmacodynamic target (PDT) that achieves 80% of maximum efficacy. First, in the mouse model of chronic TB, the PK/PD index for delamanid efficacy was determined to be area under the drug concentration-time curve over 24 h divided by MIC (AUC_{0-24}/MIC), with a PDT of 252. Second, in the hollow-fiber system model of tuberculosis, plasma-equivalent PDTs were identified as an AUC_{0-24}/MIC of 195 in log-phase bacteria and 201 in pH 5.8 cultures. Third, delamanid plasma AUC_{0-24}/MIC and sputum bacterial decline data from two early bactericidal activity trials identified a clinical PDT of AUC_{0-24}/MIC of 171. Finally, the CFRs for the currently approved 100-mg BID dose were determined to be above 95% in two MDR-TB clinical trials. The CFR for the 200-mg QD dose, evaluated in a trial in which delamanid was administered as 100 mg BID for 8 weeks plus 200 mg QD for 18 weeks, was 89.3% based on the mouse PDT and >90% on the other PDTs. QTcF (QTc interval corrected for heart rate by Fridericia's formula) prolongation was approximately 50% lower for the 200 mg QD dose than the 100 mg BID dose. In conclusion, while CFRs of 100 mg BID and 200 mg QD delamanid were close to or above 90% in patients with MDR-TB, more-convenient once-daily dosing of delamanid is feasible and likely to have less effect on QTcF prolongation.



Antimicrobial Agents and Chemotherapy

PHARMACOLOGY

Cumulative Fraction of Response for Once- and Twice-Daily Delamanid in Patients with Pulmonary Multidrug-Resistant Tuberculosis

Effectiveness and cardiovascular safety of delamanid-containing regimens in adults with multidrug-resistant or extensively drug-resistant tuberculosis: A nationwide cohort study from Belarus, 2016-18 / V. Auchynka , A. Kumar, H. et al. // Monaldi archives for chest disease. – 20212. – Vol. 91, N 1. – N 1647. DOI: 10.4081/monaldi.2021.1647

To address the sub-optimal treatment outcomes among patients with multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), the National TB Programme in Belarus started using new drugs such as bedaquiline and delamanid in 2015-16. In this study, we assessed cardiovascular safety and effectiveness (culture conversion, treatment outcomes and post-treatment recurrence) of delamanid-containing regimens among adults (>18 years) with MDR-TB or XDR-TB from June 2016 to February 2018. This was a nationwide cohort study involving analysis of routinely collected programme data from the national and six regional TB hospitals. Cardiovascular adverse events (AEs) were classified as serious or not, based on international guidelines. We conducted Cox proportional hazards regression and calculated adjusted hazards ratio(aHR) and 95% confidence intervals(CI) to evaluate factors associated with AEs and unsuccessful treatment outcomes (death, failure and lost-to-follow-up). Of 125 patients enrolled (35, 28% females; mean age 43 years), 85(68%) had XDR-TB. All the patients received delamanid and 20 patients received both delamanid and bedaquiline. Cardiovascular AEs (177 episodes in total), were observed in the majority (73%) of patients but were mild and managed easily. The most common cardiovascular AEs were QTcF prolongation (64/177, 36%) and other electrocardiography (ECG) abnormalities (40/177, 23%). There were two instances of serious AEs leading to death, both of which were not related to delamanid. In multivariable analysis, male sex (aHR 0.72; 95% CI 0.51-0.99), and baseline ECG abnormalities (aHR 1.68; 95% CI 1.19-2.36) were associated with cardiovascular AEs. Median time to culture conversion was 1.1 months (interquartile range: 1.0-2.1). Culture conversion was observed in 115 (92%) patients at six months of treatment and 110 (88%) completed the treatment successfully. Loss to follow-up, failure and death were observed in 6%, 4% and 2% patients respectively. Among those assessed at 12 months post-treatment (n=33), recurrence was seen in one patient. The only factor associated with unsuccessful treatment outcomes in multivariable analysis was baseline Hepatitis C co-infection (aHR 3.61; 95% CI 1.09-11.95). In conclusion, treatment using delamanid-containing regimens was effective and had a favourable safety profile. We hope our findings inform the development of national clinical guidelines and scale-up of new drugs in other countries.

Monaldi Archives for Chest Disease 2021; volume 91:1647

Effectiveness and cardiovascular safety of delamanid-containing regimens in adults with multidrug-resistant or extensively drug-resistant tuberculosis: A nationwide cohort study from Belarus, 2016-18

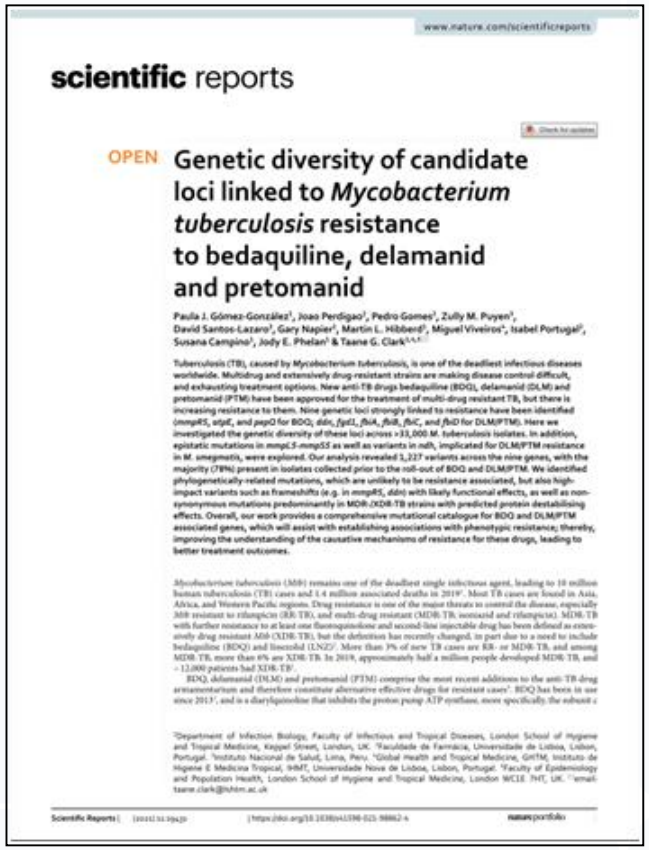
Abstract

Pecho-Silva, S. First case report in Latin America: Oral treatment of multidrug-resistant tuberculosis with delamanid and bedaquiline in combination with linezolid, moxifloxacin and clofazimine following a DRESS syndrome in a peruvian patient / S. Pecho-Silva, A. Navarro-Solsol // Pulmonology. – 2021. – Vol. 27, N 1. - P. 77 – 79. DOI:10.1016/j.pulmoe.2020.03.005

The World Health Organization recommends the use of oral medications for the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB).[1–3] However, few countries have adopted these recommendations, either due to lack of medication or because of outdated local recommendations, as in the case of Peru.[4] The combination of some medications for the treatment of MDR TB such as delamanid (Dlm) with bedaquiline (Bdq) has been associated with a potential risk of cardiovascular symptoms such as prolongation of the QT interval corrected by Fridericia interval (QTcF).[5] Other medications that may enhance the prolongation of this interval are fluroquinolones, especially moxifloxacin (Mfx) and clofazimine (Cfz). We present a case of the simultaneous use of these medications in a patient who provided informed consent. There was no prolongation of the QTcF interval, and no significant cardiac symptoms were observed throughout the entire treatment. (1) This patient was the first Peruvian to receive a completely oral combination of medications for the treatment of MDR tuberculosis.[8] (2) This was the first Peruvian case to receive a combination of 4 drugs (Mfx, Bdq, Cfz, and Dlm) considered potentially dangerous because of their sum effects on QTcF.

Genetic diversity of candidate loci linked to Mycobacterium tuberculosis resistance to bedaquiline, delamanid and pretomanid / P. Gomez-Gonzalez, J. Perdigao, P. et al. // Scientific reports. – 2021. – Vol. 11, N 1. – N 19431. DOI: 10.1038/s41598-021-98862-4

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is one of the deadliest infectious diseases worldwide. Multidrug and extensively drug-resistant strains are making disease control difficult, and exhausting treatment options. New anti-TB drugs bedaquiline (BDQ), delamanid (DLM) and pretomanid (PTM) have been approved for the treatment of multi-drug resistant TB, but there is increasing resistance to them. Nine genetic loci strongly linked to resistance have been identified (mmpR5, atpE, and pepQ for BDQ; ddn, fgd1, fbiA, fbiB, fbiC, and fbiD for DLM/PTM). Here we investigated the genetic diversity of these loci across >33,000 M. tuberculosis isolates. In addition, epistatic mutations in mmpL5-mmpS5 as well as variants in ndh, implicated for DLM/PTM resistance in M. smegmatis, were explored. Our analysis revealed 1,227 variants across the nine genes, with the majority (78%) present in isolates collected prior to the roll-out of BDQ and DLM/PTM. We identified phylogenetically-related mutations, which are unlikely to be resistance associated, but also high-impact variants such as frameshifts (e.g. in mmpR5, ddn) with likely functional effects, as well as non-synonymous mutations predominantly in MDR-/XDR-TB strains with predicted protein destabilising effects. Overall, our work provides a comprehensive mutational catalogue for BDQ and DLM/PTM associated genes, which will assist with establishing associations with phenotypic resistance; thereby, improving the understanding of the causative mechanisms of resistance for these drugs, leading to better treatment outcomes.



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Genetic diversity of candidate loci linked to *Mycobacterium tuberculosis* resistance to bedaquiline, delamanid and pretomanid

Mechanism of Action, Resistance, Synergism, and Clinical Implications of Delamanid Against Multidrug-Resistant Mycobacterium tuberculosis / S. Khoshnood, E. Taki, N. Sadeghifard // Frontiers in microbiology. – 2021. – Vol. 12. – N 717045. DOI: 10.3389/fmicb.2021.717045

Multidrug-resistant (MDR) isolates of *Mycobacterium tuberculosis* (MTB) remain a primary global threat to the end of tuberculosis (TB) era. Delamanid (DLM) is a nitro-dihydro-imidazooxazole derivative utilized to treat MDR-TB. DLM has distinct mechanism of action, inhibiting methoxy- and keto-mycolic acid (MA) synthesis through the F420 coenzyme mycobacteria system and generating nitrous oxide. While DLM resistance among MTB strains is uncommon, there are increasing reports in Asia and Europe, and such resistance will prolong the treatment courses of patients infected with MDR-TB. In this review, we address the antimycobacterial properties of DLM, report the global prevalence of DLM resistance, discuss the synergism of DLM with other anti-TB drugs, and evaluate the documented clinical trials to provide new insights into the clinical use of this antibiotic.

frontiers in Microbiology

Mechanism of Action, Resistance, Synergism, and Clinical Implications of Delamanid Against Multidrug-Resistant *Mycobacterium tuberculosis*

INTRODUCTION

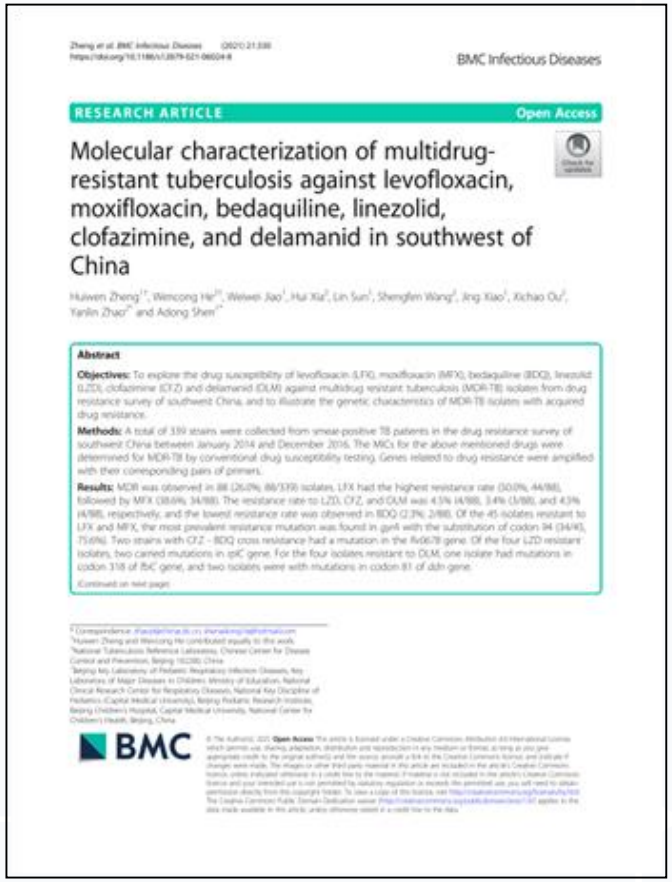
Molecular characterization of multidrug-resistant tuberculosis against levofloxacin, moxifloxacin, bedaquiline, linezolid, clofazimine, and delamanid in southwest of China / H. Zheng, W. He, W. et al. // BMC infectious diseases. – 2021. – Vol. 21, N 1. – N 330. DOI: 10.1186/s12879-021-06024-8

Objectives: To explore the drug susceptibility of levofloxacin (LFX), moxifloxacin (MFX), bedaquiline (BDQ), linezolid (LZD), clofazimine (CFZ) and delamanid (DLM) against multidrug resistant tuberculosis (MDR-TB) isolates from drug resistance survey of southwest China, and to illustrate the genetic characteristics of MDR-TB isolates with acquired drug resistance.

Methods: A total of 339 strains were collected from smear-positive TB patients in the drug resistance survey of southwest China between January 2014 and December 2016. The MICs for the above mentioned drugs were determined for MDR-TB by conventional drug susceptibility testing. Genes related to drug resistance were amplified with their corresponding pairs of primers.

Results: MDR was observed in 88 (26.0%; 88/339) isolates. LFX had the highest resistance rate (50.0%; 44/88), followed by MFX (38.6%; 34/88). The resistance rate to LZD, CFZ, and DLM was 4.5% (4/88), 3.4% (3/88), and 4.5% (4/88), respectively, and the lowest resistance rate was observed in BDQ (2.3%; 2/88). Of the 45 isolates resistant to LFX and MFX, the most prevalent resistance mutation was found in gyrA with the substitution of codon 94 (34/45, 75.6%). Two strains with CFZ - BDQ cross resistance had a mutation in the Rv0678 gene. Of the four LZD resistant isolates, two carried mutations in rplC gene. For the four isolates resistant to DLM, one isolate had mutations in codon 318 of fbiC gene, and two isolates were with mutations in codon 81 of ddn gene.

Conclusion: This study provided evidence of the usefulness of new anti-TB drugs in the treatment of MDR-TB in China.



BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Molecular characterization of multidrug-resistant tuberculosis against levofloxacin, moxifloxacin, bedaquiline, linezolid, clofazimine, and delamanid in southwest of China

BMC

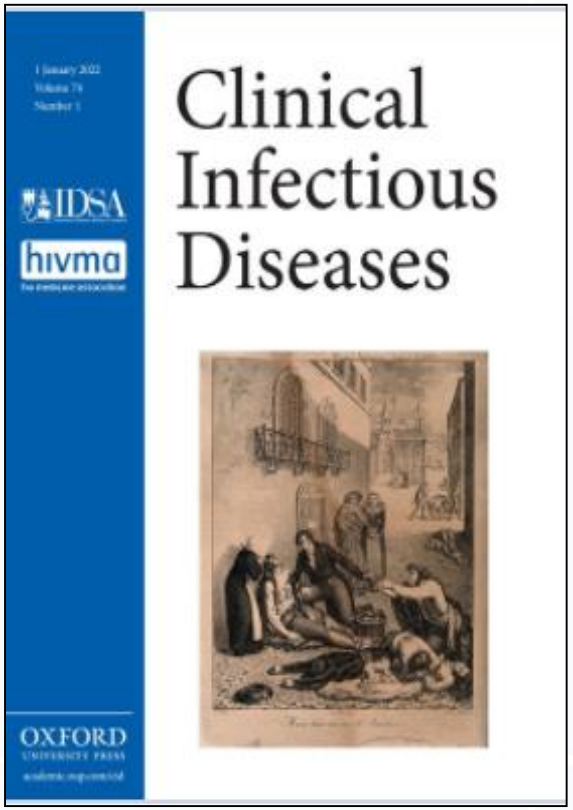
One Step Forward: Successful End-of-Treatment Outcomes of Patients With Drug-Resistant Tuberculosis Who Received Concomitant Bedaquiline and Delamanid in Mumbai, India / M. Das, A. Dalal, C. Laxmeshwar et al. // Clinical infectious diseases. – 2021. – Vol. 73, N 9. - P. E3496 - E3504. DOI: 10.1093/cid/ciaa1577

Background: The Médecins Sans Frontières Clinic in Mumbai, India, has been providing concomitant bedaquiline (BDQ) and delamanid (DLM) in treatment regimen for patients with drug-resistant tuberculosis (DR-TB) and limited therapeutic options, referred from other healthcare institutions, since 2016. The study documents the end-of-treatment outcomes, culture-conversion rates, and serious adverse events (SAEs) during treatment.

Methods: This was a retrospective cohort study based on routinely collected program data. In clinic, treatment regimens are designed based on culture drug sensitivity test patterns and previous drug exposures, and are provided for 20-22 months. BDQ and DLM are extended beyond 24 weeks as off-label use. Patients who initiated DR-TB treatment including BDQ and DLM (concomitantly for at least 4 weeks) during February 2016-February 2018 were included.

Results: Of the 70 patients included, the median age was 25 (interquartile range [IQR], 22-32) years and 56% were females. All except 1 were fluoroquinolone resistant. The median duration of exposure to BDQ and DLM was 77 (IQR, 43-96) weeks. Thirty-nine episodes of SAEs were reported among 30 (43%) patients, including 5 instances of QTc prolongation, assessed as possibly related to BDQ and/or DLM. The majority (69%) had culture conversion before 24 weeks of treatment. In 61 (87%), use of BDQ and DLM was extended beyond 24 weeks. Successful end-of-treatment outcomes were reported in 49 (70%) patients.

Conclusions: The successful treatment outcomes of this cohort show that regimens including concomitant BDQ and DLM for longer than 24 weeks are effective and can be safely administered on an ambulatory basis. National TB programs globally should scale up access to life-saving DR-TB regimens with new drugs.

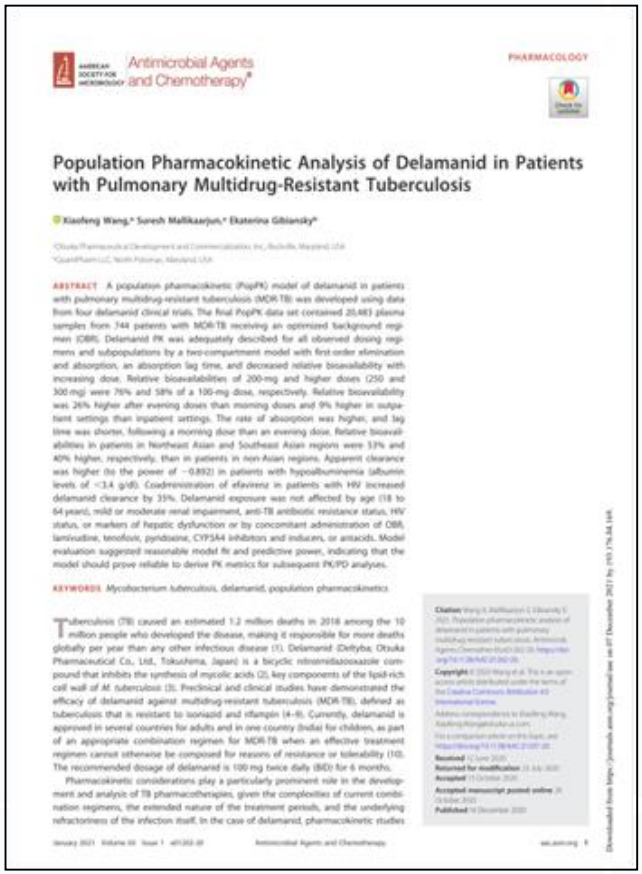


Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid: Results from a large global cohort / S. Kpirala, S. Borisov, E. Danila et al. // Pulmonology. – 2021. – Vol. 27, N 5. - P. 403 – 412. DOI: 10.1016/j.pulmoe.2021.02.006

The World Health Organization (WHO) recommends countries introduce new anti-TB drugs in the treatment of multidrug-resistant tuberculosis. The aim of the study is to prospectively evaluate the effectiveness of bedaquiline (and/or delamanid)- containing regimens in a large cohort of consecutive TB patients treated globally. This observational, prospective study is based on data collected and provided by Global Tuberculosis Network (GTN) centres and analysed twice a year. All consecutive patients (including children/adolescents) treated with bedaquiline and/or delamanid were enrolled, and managed according to WHO and national guidelines. Overall, 52 centres from 29 countries/regions in all continents reported 883 patients as of January 31st 2021, 24/29 countries/regions providing data on 100% of their consecutive patients (10-80% in the remaining 5 countries). The drug-resistance pattern of the patients was severe (>30% with extensively drug-resistant -TB; median number of resistant drugs 5 (3-7) in the overall cohort and 6 (4-8) among patients with a final outcome). For the patients with a final outcome (477/883, 54.0%) the median (IQR) number of months of anti-TB treatment was 18 (13-23) (in days 553 (385-678)). The proportion of patients achieving sputum smear and culture conversion ranged from 93.4% and 92.8% respectively (whole cohort) to 89.3% and 88.8% respectively (patients with a final outcome), a median (IQR) time to sputum smear and culture conversion of 58 (30-90) days for the whole cohort and 60 (30-100) for patients with a final outcome and, respectively, of 55 (30-90) and 60 (30-90) days for culture conversion. Of 383 patients treated with bedaquiline but not delamanid, 284 (74.2%) achieved treatment success, while 25 (6.5%) died, 11 (2.9%) failed and 63 (16.5%) were lost to follow-up.

Wang, X. Population Pharmacokinetic Analysis of Delamanid in Patients with Pulmonary Multidrug-Resistant Tuberculosis / X. Wang, S. Mallikaarjun, E. Gibiansky // Antimicrobial agents and chemotherapy. – 2021. – Vol. 65, N 1. – N e01202-20. DOI: 10.1128/AAC.01202-20

A population pharmacokinetic (PopPK) model of delamanid in patients with pulmonary multidrug-resistant tuberculosis (MDR-TB) was developed using data from four delamanid clinical trials. The final PopPK data set contained 20,483 plasma samples from 744 patients with MDR-TB receiving an optimized background regimen (OBR). Delamanid PK was adequately described for all observed dosing regimens and subpopulations by a two-compartment model with first-order elimination and absorption, an absorption lag time, and decreased relative bioavailability with increasing dose. Relative bioavailabilities of 200-mg and higher doses (250 and 300 mg) were 76% and 58% of a 100-mg dose, respectively. Relative bioavailability was 26% higher after evening doses than morning doses and 9% higher in outpatient settings than inpatient settings. The rate of absorption was higher, and lag time was shorter, following a morning dose than an evening dose. Relative bioavailabilities in patients in Northeast Asian and Southeast Asian regions were 53% and 40% higher, respectively, than in patients in non-Asian regions. Apparent clearance was higher (to the power of -0.892) in patients with hypoalbuminemia (albumin levels of <3.4 g/dl). Coadministration of efavirenz in patients with HIV increased delamanid clearance by 35%. Delamanid exposure was not affected by age (18 to 64 years), mild or moderate renal impairment, anti-TB antibiotic resistance status, HIV status, or markers of hepatic dysfunction or by concomitant administration of OBR, lamivudine, tenofovir, pyridoxine, CYP3A4 inhibitors and inducers, or antacids. Model evaluation suggested reasonable model fit and predictive power, indicating that the model should prove reliable to derive PK metrics for subsequent PK/PD analyses.



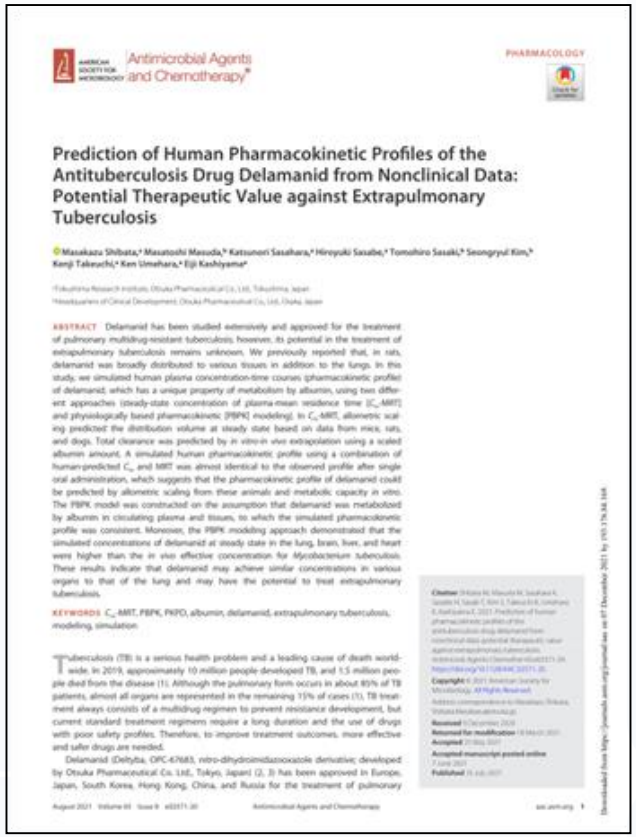
Antimicrobial Agents and Chemotherapy

PHARMACOLOGY

Population Pharmacokinetic Analysis of Delamanid in Patients with Pulmonary Multidrug-Resistant Tuberculosis

Prediction of Human Pharmacokinetic Profiles of the Antituberculosis Drug Delamanid from Nonclinical Data: Potential Therapeutic Value against Extrapulmonary Tuberculosis / M. Shibata, M. Masuda, K. Sasahara et al. // Antimicrobial agents and chemotherapy. - 2021. – Vol. 65, N 8. - e02571-20. DOI:10.1128/AAC.02571-20

Delamanid has been studied extensively and approved for the treatment of pulmonary multidrug-resistant tuberculosis; however, its potential in the treatment of extrapulmonary tuberculosis remains unknown. We previously reported that, in rats, delamanid was broadly distributed to various tissues in addition to the lungs. In this study, we simulated human plasma concentration-time courses (pharmacokinetic profile) of delamanid, which has a unique property of metabolism by albumin, using two different approaches (steady-state concentration of plasma-mean residence time [C_{ss}-MRT] and physiologically based pharmacokinetic [PBPK] modeling). In C_{ss}-MRT, allometric scaling predicted the distribution volume at steady state based on data from mice, rats, and dogs. Total clearance was predicted by *in vitro-in vivo* extrapolation using a scaled albumin amount. A simulated human pharmacokinetic profile using a combination of human-predicted C_{ss} and MRT was almost identical to the observed profile after single oral administration, which suggests that the pharmacokinetic profile of delamanid could be predicted by allometric scaling from these animals and metabolic capacity *in vitro*. The PBPK model was constructed on the assumption that delamanid was metabolized by albumin in circulating plasma and tissues, to which the simulated pharmacokinetic profile was consistent. Moreover, the PBPK modeling approach demonstrated that the simulated concentrations of delamanid at steady state in the lung, brain, liver, and heart were higher than the *in vivo* effective concentration for Mycobacterium tuberculosis. These results indicate that delamanid may achieve similar concentrations in various organs to that of the lung and may have the potential to treat extrapulmonary tuberculosis.



Antimicrobial Agents and Chemotherapy

PHARMACOLOGY

Prediction of Human Pharmacokinetic Profiles of the Antituberculosis Drug Delamanid from Nonclinical Data: Potential Therapeutic Value against Extrapulmonary Tuberculosis

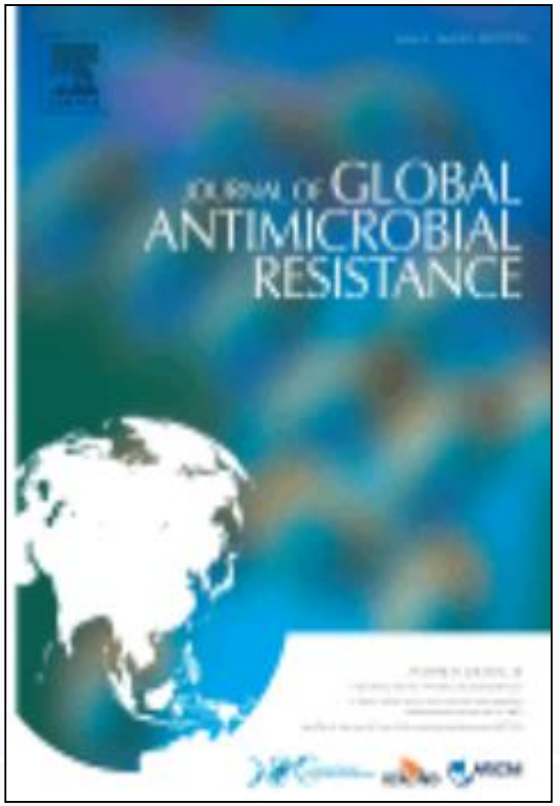
Prevalence of Mycobacterium tuberculosis resistant to bedaquiline and delamanid in China / W. He, C. Liu, D. Liu et al. // Journal of global antimicrobial resistance . – 2021. – Vol. 26 . - P. 241 – 248. DOI: 10.1016/j.jgar.2021.06.007

Objectives: The new antituberculous drugs delamanid and bedaquiline form the last line of defence against drug-resistant tuberculosis (TB). Understanding the background prevalence of resistance to new drugs can help predict the lifetime of these drugs' effectiveness and inform regimen design.

Methods: Mycobacterium tuberculosis without prior exposure to novel anti-TB drugs were analysed retrospectively. Drug susceptibility testing for bedaquiline, delamanid, linezolid, clofazimine and widely used first- and second-line anti-TB drugs was performed. All TB isolates with resistance to new or repurposed drugs were subjected to whole-genome sequencing to explore the molecular characteristics of resistance and to perform phylogenetic analysis.

Results: Overall, resistance to delamanid, bedaquiline, linezolid and clofazimine was observed in 0.7% (11/1603), 0.4% (6/1603), 0.4% (7/1603) and 0.4% (6/1603) of TB isolates, respectively. Moreover, 1.0% (1/102), 2.9% (3/102), 3.9% (4/102) and 1.0% (1/102) of multidrug-resistant TB (MDR-TB) were resistant to bedaquiline, delamanid, linezolid and clofazimine, respectively. Whereas 22.2% (2/9) of extensively-drug resistant tuberculosis (XDR-TB) isolates were resistant to both delamanid and linezolid, and none was resistant to bedaquiline or clofazimine. Phylogenetic analysis showed that recent transmission occurred in two XDR-TB with additional resistance to delamanid and linezolid. None known gene mutation associated with delamanid resistance was detected. All four isolates with cross-resistance to bedaquiline and clofazimine had a detected gene mutation in Rv0678. Three of five strains with linezolid resistance had a detected gene mutation in rplC.

Conclusion: Detection of resistance to new anti-TB drugs emphasises the pressing need for intensive surveillance for such resistance before their wide usage.



Sustained absorption of delamanid from lipid-based formulations as a path to reduced frequency of administration / G. Ramirez, A. Pham, A. Clulow et al. // Drug delivery and translational research. – 2021. – Vol. 11, N 3. - P. 1236 – 1244. DOI10.1007/s13346-020-00851-z

Delamanid is a poorly water-soluble drug currently being used for the treatment of tuberculosis. The high frequency of dosing leads to poor adherence for patients who live in lower economic and nomadic populations. Non-digestible self-assembling lipids as a formulation approach for poorly water-soluble drugs have previously been shown to extend the window of absorption through gastric retention. We hypothesise that this approach could lead to the reduction of dosing frequency for delamanid and thereby has potential to improve adherence. Formulations of delamanid were prepared in selachyl alcohol and phytantriol as non-digestible self-assembling lipid vehicles, and their behaviour was compared with reconstituted milk powder, as a digestible lipid-based formulation, and an aqueous suspension. The self-assembly of selachyl alcohol and phytantriol in aqueous media in the presence of delamanid was studied using small angle X-ray scattering and produced the inverse hexagonal (H_2) and inverse bicontinuous cubic (V_2) liquid crystal structures, respectively. The times at which maximum delamanid levels in plasma were observed (T_{max}) after oral administration of the phytantriol, selachyl alcohol and reconstituted milk powder formulations of delamanid to rats were 27 ± 3, 20 ± 4 and 6.5 ± 1.0 h, respectively, compared with the aqueous suspension formulation with a T_{max} of 3.4 ± 1 h, which confirms the hypothesis of an extended duration of absorption after administration in non-digestible self-assembling lipids. The digestion products of the triglycerides in the milk formulation increased the solubilisation of delamanid in the gastrointestinal tract, leading to an increase in exposure compared with the aqueous suspension formulation but did not significantly extend T_{max}. Overall, the non-digestible nanostructured lipid formulations extended the duration of absorption of delamanid well beyond that from milk or suspension formulations. Graphical abstract.