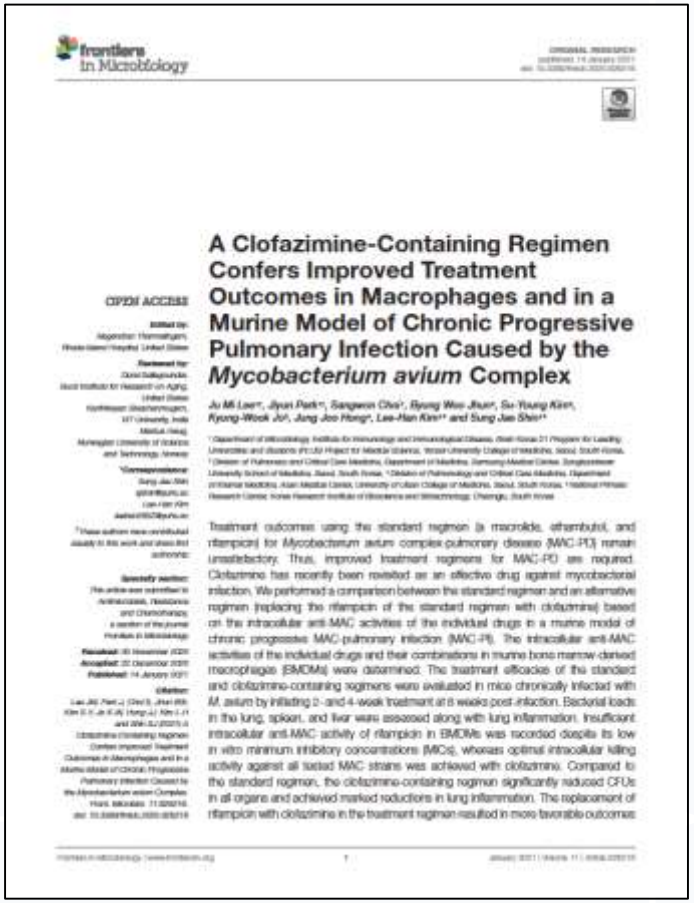
Клофазимин – новый противотуберкулезный препарат. Зарубежные исследования

A Clofazimine-Containing Regimen Confers Improved Treatment Outcomes in Macrophages and in a Murine Model of Chronic Progressive Pulmonary Infection Caused by the Mycobacterium avium Complex / J. Lee, J. Park, S. Choi [et al.] // Front Microbiol. – 2021. – Vol 14. – N 626216. doi: 10.3389/fmicb.2020.626216. eCollection 2020.

Treatment outcomes using the standard regimen (a macrolide, ethambutol, and rifampicin) for *Mycobacterium avium* complex-pulmonary disease (MAC-PD) remain unsatisfactory. Thus, improved treatment regimens for MAC-PD are required. Clofazimine has recently been revisited as an effective drug against mycobacterial infection. We performed a comparison between the standard regimen and an alternative regimen (replacing the rifampicin of the standard regimen with clofazimine) based on the intracellular anti-MAC activities of the individual drugs in a murine model of chronic progressive MAC-pulmonary infection (MAC-PI). The intracellular anti-MAC activities of the individual drugs and their combinations in murine bone marrow-derived macrophages (BMDMs) were determined. The treatment efficacies of the standard and clofazimine-containing regimens were evaluated in mice chronically infected with *M. avium* by initiating 2- and 4-week treatment at 8 weeks post-infection. Bacterial loads in the lung, spleen, and liver were assessed along with lung inflammation. Insufficient intracellular anti-MAC activity of rifampicin in BMDMs was recorded despite its low *in vitro* minimum inhibitory concentrations (MICs), whereas optimal intracellular killing activity against all tested MAC strains was achieved with clofazimine. Compared to the standard regimen, the clofazimine-containing regimen significantly reduced CFUs in all organs and achieved marked reductions in lung inflammation. The replacement of rifampicin with clofazimine in the treatment regimen resulted in more favorable outcomes in an animal model of chronic progressive MAC-PI. Intriguingly, 2 weeks of treatment with the clofazimine-containing regimen reduced bacterial loads more effectively than 4 weeks of treatment with the standard regimen in M. av/um-infected mice. Thus, the clofazimine-containing regimen also had a treatment-shortening effect.



frontiers in Microbiology

ORIGINAL RESEARCH

OPEN ACCESS

A Clofazimine-Containing Regimen Confers Improved Treatment Outcomes in Macrophages and in a Murine Model of Chronic Progressive Pulmonary Infection Caused by the *Mycobacterium avium* Complex

Ju Mi Lee[†], Jiyun Park[†], Sangeon Choi[†], Byung Woo Jhun[†], Su-Young Kim[†], Kyung-Wook Jo[†], Jung Joo Hong[†], Lee-Han Kim[*†] and Sung Jae Shin[*†]

Treatment outcomes using the standard regimen (a macrolide, ethambutol, and rifampicin) for *Mycobacterium avium* complex-pulmonary disease (MAC-PD) remain unsatisfactory. Thus, improved treatment regimens for MAC-PD are required. Clofazimine has recently been revisited as an effective drug against mycobacterial infection. We performed a comparison between the standard regimen and an alternative regimen (replacing the rifampicin of the standard regimen with clofazimine) based on the intracellular anti-MAC activities of the individual drugs in a murine model of chronic progressive MAC-pulmonary infection (MAC-PI). The intracellular anti-MAC activities of the individual drugs and their combinations in murine bone marrow-derived macrophages (BMDMs) were determined. The treatment efficacies of the standard and clofazimine-containing regimens were evaluated in mice chronically infected with *M. avium* by initiating 2- and 4-week treatment at 8 weeks post-infection. Bacterial loads in the lung, spleen, and liver were assessed along with lung inflammation. Insufficient intracellular anti-MAC activity of rifampicin in BMDMs was recorded despite its low *in vitro* minimum inhibitory concentrations (MICs), whereas optimal intracellular killing activity against all tested MAC strains was achieved with clofazimine. Compared to the standard regimen, the clofazimine-containing regimen significantly reduced CFUs in all organs and achieved marked reductions in lung inflammation. The replacement of rifampicin with clofazimine in the treatment regimen resulted in more favorable outcomes

Acquisition of clofazimine resistance following bedaquiline treatment for multidrug-resistant tuberculosis / Y. Liu, J. Gao, J. Du [et al.] // Int. J. Infect. Dis. – 2021. – Vol. 102. – P. 392 – 396. doi: 10.1016/j.ijid.2020.10.081. Epub 2020 Oct 29.

Objectives: The aim of this study was to describe the prevalence of clofazimine (CFZ) resistance in a cohort of patients with multidrug-resistant tuberculosis (MDR-TB) in China. A further aim was to identify dynamic changes in CFZ susceptibility and its molecular mechanism after exposure to bedaquiline (BDQ) and/or CFZ.

Methods: The experimental setting was based on an MDR-TB cohort receiving BDQ-containing regimens. Sequential isolates were obtained from these patients. The CFZ and BDQ susceptibility of isolates were determined using the minimum inhibitory concentration (MIC) method. The fragments of *Rv0678* and *pepQ* were sequenced.

Results: A total of 277 patients infected with MDR-TB were included in this study. CFZ resistance was noted in 23 isolates (23/277, 8.3%). The rate of acquired CFZ resistance (12/189, 6.3%) was significantly greater than that of primary resistance (11/88,12.5%, $p = 0.028$). Out of 23 CFZ-resistant isolates, five (5/ 23) were BDQ-resistant and the other 18 (18/23) were susceptible to BDQ. Of note, nine out of 23 CFZ-resistant isolates had mutations within either of the target genes. Kaplan-Meier analysis demonstrated that the baseline CFZ resistance had no influence on time to culture conversion in this cohort ($p = 0.828$). Acquired CFZ resistance emerged in eight patients (8/94, 8.5%) during treatment for MDR-TB, including three patients receiving regimens without CFZ.

Conclusions: The study results demonstrated a high rate of CFZ resistance among MDR-TB patients in China. Patients treated with BDQ-containing regimens achieved a comparable culture conversion rate regardless of baseline CFZ susceptibility. The presence of acquired CFZ resistance following BDQ treatment without a known mutation indicates that other mechanisms conferring cross-resistance to these two compounds may exist.

International Journal of Infectious Diseases

Acquisition of clofazimine resistance following bedaquiline treatment for multidrug-resistant tuberculosis

Activity of Clofazimine and TBI-166 against Mycobacterium tuberculosis in Different Administration Intervals in Mouse Tuberculosis Models / H. Zhun, L. Fu, B. Wang [et al.] // Antimicrob. Agents Chemother. – 2020. – Vol. 65, N 4. – N e02164-20. doi: 10.1128/AAC.02164-20. Print 2021

Clofazimine (CLO) and TBI-166 belong to the riminophenazine class of antimicrobial agent. TBI-166 exhibited promising antituberculosis activity *in vitro* and in animal models and is currently under phase I clinical development for the treatment of tuberculosis in China. To identify an optimal dosing regimen to support further clinical development of TBI-166, the efficacies of CLO and TBI-166 were evaluated in two aerosol infection models utilizing BALB/c and C3HeB/FeJNju mice. TBI-166 and CLO were dosed at 20 mg/kg daily for 2 weeks, followed by QD (once daily), TIW (thrice weekly), and BIW (twice weekly) for an additional 10 weeks at the same dose level. The bactericidal activities of TBI-166 and clofazimine via QD, TIW, and BIW dosing regimens were determined after treatment. Once-daily administration of CLO and TBI-166 appeared to be more efficacious than the two intermittent dosing regimens. Once-daily administration of TBI-166 increased the bactericidal activity by approximately 1 $\log_{10}$ CFU in the lung and spleen compared with TIW or BIW dosing after 12 weeks of treatment, while once-daily administration of CLO increased the bactericidal activity by 1.27 to 1.90 $\log_{10}$ CFU/lung and by 1.61 to 2.22 $\log_{10}$ CFU/ spleen in the BALB/c mouse model compared to the intermittent therapies. The differences between QD and TIW and between QD and BIW were significant *(P* < 0.05). The data suggest that accumulated total doses correlate with the $\log_{10}$ CFU reductions. Therefore, intermittent administration of TBI-166 and CLO should be further evaluated at the same accumulated total doses in preclinical and clinical studies.

Antimicrobial Agents and Chemotherapy

EXPERIMENTAL THERAPEUTICS

Activity of Clofazimine and TBI-166 against *Mycobacterium tuberculosis* in Different Administration Intervals in Mouse Tuberculosis Models

Clofazimine inhalation suspension for the aerosol treatment of pulmonary nontuberculous mycobacterial infections / B. Banaschewski, D. Verma, I. Pennings [et al.] // J. Cyst. Fibros. – 2019. – Vol. 5. – P. 714 – 720. doi: 10.1016/j.jcf.2019.05.013. Epub 2019 May 25.

Background: Nontuberculous mycobacteria are recognized as a concern for cystic fibrosis (CF) patients due to increasing disease prevalence and the potential for detrimental effects on pulmonary function and mortality. Current standard of care involves prolonged systemic antibiotics, which often leads to severe side effects and poor treatment outcomes. In this study, we investigated the tolerability and efficacy of a novel inhaled therapeutic in various mouse models of NTM disease.

Methods: We developed clofazimine inhalation suspension (CIS), a novel formulation of clofazimine developed for inhaled administration. To determine the efficacy, minimum inhibitory concentrations were evaluated in vitro, and tolerability of CIS was determined in naive mouse models over various durations. After establishing tolerability, CIS efficacy was tested in in vivo infection models of both *Mycobacterium avium* and *M. abscessus.* Lung and plasma clofazimine levels after chronic treatments were evaluated.

Results: Clofazimine inhalation suspension demonstrated antimycobacterial activity in vitro, with MIC values between 0.125 and 2 ug/ml for *M. avium* complex and *M. abscessus.* Administration into naive mice showed that CIS was well tolerated at doses up to 28 mg/kg over 28 consecutive treatments. In vivo, CIS was shown to significantly improve bacterial elimination from the lungs of both acute and chronic NTM-infected mouse models compared to negative controls and oral clofazimine administration. Clofazimine concentrations in lung tissue were approximately four times higher than the concentrations achieved by oral dosing. *Conclusion:* Clofazimine inhalation suspension is a well tolerated and effective novel therapeutic candidate for the treatment of NTM infections in mouse models.

Journal of Cystic Fibrosis

Original Article

Clofazimine inhalation suspension for the aerosol treatment of pulmonary nontuberculous mycobacterial infections

Clofazimine susceptibility testing of Mycobacterium avium complex and Mycobacterium abscessus: a meta-analysis study / B. Hajikhani, M. Nasiri, S. Hosseini [et al.] // J. Glob. Antimicrob. Resist. – 2021. – Vol. 26. – P. 188 – 193. doi: 10.1016/j.jgar.2021.06.002. Epub 2021 Jun 19.

Objectives: The incidence of infections due to *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* (MABS) is increasing worldwide. Current antimycobacterial agents are not sufficiently effective against nontuberculous mycobacteria (NTM) and there is a need for new drugs. This study aimed to estimate the overall in vitro activity of clofazimine (CFZ) against MAC and MABS clinical isolates.

Methods: We systematically searched four databases up to 1 March 2020 to identify relevant studies. Studies were included if they used the Clinical and Laboratory Standards Institute (CLSI) criteria for drug susceptibility testing (DST). We assessed the pooled in vitro CFZ resistance rate in MAC and MABS clinical isolates using a random- effects model. Sources of heterogeneity were evaluated using Cochran's Q and the I^2 statistic. Potential for publication bias was explored using Begg's and Egger's tests. All analyses were conducted using Stata 14.0.

Results: A total of 20 publications (11 reports for MAC and 15 for MABS) were included. The pooled rates of in vitro resistance to CFZ in clinical isolates of MAC and MABS were 9.0% [95% confidence interval (CI) 3.0-17.0%] and 16.0% (95% CI 4.0-34.0%), respectively. There was no evidence of publication bias.

Conclusion: This study reports the frequency of CFZ resistance in clinical isolates of MAC and MABS. According to the results, establishing accurate DST methods for detecting CFZ resistance, performing DST for all NTM isolates to provide effective treatment, and continuous monitoring of drug resistance are suggested for the prevention and control of CFZ-resistant NTM.

Journal of Global Antimicrobial Resistance

Review

Clofazimine susceptibility testing of *Mycobacterium avium* complex and *Mycobacterium abscessus*: a meta-analysis study

Effect of Clofazimine Concentration on QT Prolongation in Patients Treated for Tuberculosis / M. Abdelwahab, R. Court, D. Everitt [et al.] // Antimicrob. Agents Chemother. – 2021. – Vol. 65, N 7. – N e0268720. doi: 10.1128/AAC.02687-20. Epub 2021 Jun 17.

Clofazimine is classified as a WHO group B drug for the treatment of rifampin-resistant tuberculosis. QT prolongation, which is associated with fatal cardiac arrhythmias, is caused by several antitubercular drugs, including clofazimine, but there are no data quantifying the effect of clofazimine concentration on QT prolongation. Our objective was to describe the effect of clofazimine exposure on QT prolongation. Fifteen adults drug-susceptible tuberculosis patients received clofazimine monotherapy as 300 mg daily for 3 days, followed by 100 mg daily in one arm of a 2-week, multiarm early bactericidal activity trial in South Africa. Pretreatment Fridericia-corrected QT (QTcF) (105 patients, 524 electrocardiograms [ECGs]) and QTcFs from the clofazimine monotherapy arm matched with clofazimine plasma concentrations (199 ECGs) were interpreted with a nonlinear mixed-effects model. Clofazimine was associated with significant QT prolongation described by a maximum effect (E_{max}) function. We predicted clofazimine exposures using 100-mg daily doses and 2 weeks of loading with 200 and 300 mg daily, respectively. The expected proportions of patients with QTcF change from baseline above 30 ms (DQTcF > 30) were 2.52%, 11.6%, and 23.0% for 100-, 200-, and 300-mg daily doses, respectively. At steady state, the expected proportion with DQTcF of >30 ms was 23.7% and with absolute QTcF of >450 ms was 3.42% for all simulated regimens. The use of loading doses of 200 and 300 mg is not predicted to expose patients to an increased risk of QT prolongation, compared with the current standard treatment, and is, therefore, an alternative option for more quickly achieving therapeutic concentrations.

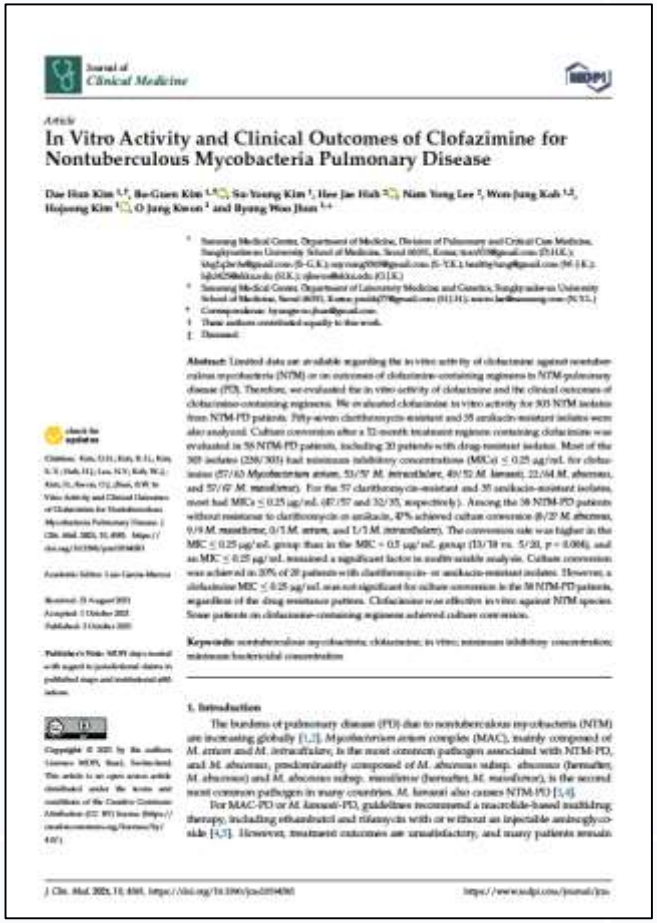
Antimicrobial Agents and Chemotherapy

CLINICAL THERAPEUTICS

Effect of Clofazimine Concentration on QT Prolongation in Patients Treated for Tuberculosis

In Vitro Activity and Clinical Outcomes of Clofazimine for Nontuberculous Mycobacteria Pulmonary Disease / D. Kim, B. Kim, S. Kim S. [et al.] // J. Clin. Med. – 2021. – Vol.10, N 19. – N 4581. doi: 10.3390/jcm10194581.

Limited data are available regarding the in vitro activity of clofazimine against nontuberculous mycobacteria (NTM) or on outcomes of clofazimine-containing regimens in NTM-pulmonary disease (PD). Therefore, we evaluated the in vitro activity of clofazimine and the clinical outcomes of clofazimine-containing regimens. We evaluated clofazimine in vitro activity for 303 NTM isolates from NTM-PD patients. Fifty-seven clarithromycin-resistant and 35 amikacin-resistant isolates were also analyzed. Culture conversion after a 12-month treatment regimen containing clofazimine was evaluated in 58 NTM-PD patients, including 20 patients with drug-resistant isolates. Most of the 303 isolates (238/303) had minimum inhibitory concentrations (MICs) < 0.25 ug/mL for clofazimine (57/63 *Mycobacterium avium,* 53/57 M. *intracellulare,* 49/52 M. *kansasii,* 22/64 M. *abscessus,* and 57/67 *M. massiliense).* For the 57 clarithromycin-resistant and 35 amikacin-resistant isolates, most had MICs < 0.25 ug/mL (47/57 and 32/35, respectively). Among the 38 NTM-PD patients without resistance to clarithromycin or amikacin, 47% achieved culture conversion (8/27 *M. abscessus,* 9/9 *M. massiliense,* 0/1 *M. avium,* and 1/1 *M. intracellulare).* The conversion rate was higher in the
MIC < 0.25 | g/mL group than in the MIC = 0.5 | g/mL group (13/18 vs. 5/20, p = 0.004), and
an MIC < 0.25 ug/mL remained a significant factor in multivariable analysis. Culture conversion was achieved in 20% of 20 patients with clarithromycin- or amikacin-resistant isolates. However, a clofazimine MIC < 0.25 ug/mL was not significant for culture conversion in the 58 NTM-PD patients, regardless of the drug resistance pattern. Clofazimine was effective in vitro against NTM species. Some patients on clofazimine-containing regimens achieved culture conversion.



Journal of Clinical Medicine

Article

In Vitro Activity and Clinical Outcomes of Clofazimine for Nontuberculous Mycobacteria Pulmonary Disease

Dae Hun Kim [1,†], Bo-Guen Kim [1,†], Su Young Kim [1], Hee Jae Huh [2], Nam Yong Lee [2], Won Jung Koh [1,3], Hojoong Kim [1], O Jung Kwon [3] and Byung Woo Jhun [1,*]

Abstract: Limited data are available regarding the in vitro activity of clofazimine against nontuberculous mycobacteria (NTM) or on outcomes of clofazimine-containing regimens in NTM-pulmonary disease (PD). Therefore, we evaluated the in vitro activity of clofazimine and the clinical outcomes of clofazimine-containing regimens. We evaluated clofazimine in vitro activity for 303 NTM isolates from NTM-PD patients. Fifty-seven clarithromycin-resistant and 35 amikacin-resistant isolates were also analyzed. Culture conversion after a 12-month treatment regimen containing clofazimine was evaluated in 58 NTM-PD patients, including 20 patients with drug-resistant isolates. Most of the 303 isolates (238/303) had minimum inhibitory concentrations (MICs) ≤ 0.25 µg/mL for clofazimine (57/63 *Mycobacterium avium*, 53/57 *M. intracellulare*, 49/52 *M. kansasii*, 22/64 *M. abscessus*, and 57/67 *M. massiliense*). For the 57 clarithromycin-resistant and 35 amikacin-resistant isolates, most had MICs ≤ 0.25 µg/mL (47/57 and 32/35, respectively). Among the 38 NTM-PD patients without resistance to clarithromycin or amikacin, 47% achieved culture conversion (8/27 *M. abscessus*, 9/9 *M. massiliense*, 0/1 *M. avium*, and 1/1 *M. intracellulare*). The conversion rate was higher in the MIC ≤ 0.25 µg/mL group than in the MIC = 0.5 µg/mL group (13/18 vs. 5/20, $p = 0.004$), and an MIC ≤ 0.25 µg/mL remained a significant factor in multivariable analysis. Culture conversion was achieved in 20% of 20 patients with clarithromycin- or amikacin-resistant isolates. However, a clofazimine MIC ≤ 0.25 µg/mL was not significant for culture conversion in the 58 NTM-PD patients, regardless of the drug resistance pattern. Clofazimine was effective in vitro against NTM species. Some patients on clofazimine-containing regimens achieved culture conversion.

Keywords: nontuberculous mycobacteria; clofazimine; in vitro; minimum inhibitory concentration; minimum bactericidal concentration

1. Introduction

The burdens of pulmonary disease (PD) due to nontuberculous mycobacteria (NTM) are increasing globally [1,2]. *Mycobacterium avium* complex (MAC), mainly composed of *M. avium* and *M. intracellulare*, is the most common pathogen associated with NTM-PD, and *M. abscessus*, predominantly composed of *M. abscessus* subsp. *abscessus* (hereafter, *M. abscessus*) and *M. abscessus* subsp. *massiliense* (hereafter, *M. massiliense*), is the second most common pathogen in many countries. *M. kansasii* also causes NTM-PD [3,4].

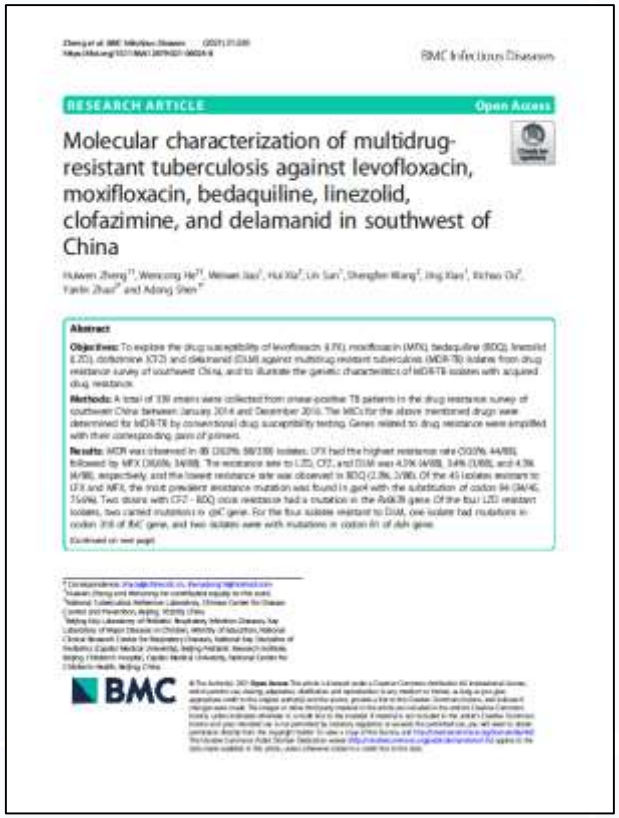
For MAC-PD or *M. kansasii*-PD, guidelines recommend a macrolide-based multidrug therapy, including ethambutol and rifamycin with or without an injectable aminoglycoside [4,5]. However, treatment outcomes are unsatisfactory, and many patients remain

Molecular characterization of multidrug-resistant tuberculosis against levofloxacin, moxifloxacin, bedaquiline, linezolid, clofazimine, and delamanid in southwest of China / H. Zheng, W. He, W. Jiao [et al.] // BMC Infect. Dis. -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 rp/C 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.



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

Novel Mutations Associated with Clofazimine Resistance in Mycobacterium abscessus / Y. Chen, J. Chen, S. Zhang S. [et al.] // Antimicrob. Agents Chemother. – 2018. – Vol. 62, N 7. – N e00544-18. doi:10.1128/AAC.00544-18.

Mycobacterium abscessus is a major nontuberculous mycobacterial (NTM) pathogen and is responsible for about 80% of all pulmonary infections caused by rapidly growing mycobacteria. Clofazimine is an effective drug active against *M. abscessus,* but the mechanism of resistance to clofazimine in *M. abscessus* is unknown. To investigate the molecular basis of clofazimine resistance in *M. abscessus,* we isolated 29 *M. abscessus* mutants resistant to clofazimine and subjected them to whole-genome sequencing to identify possible mutations associated with clofazimine resistance. We found that mutations in the MAB_2299c gene (which encodes a possible transcriptional regulatory protein), MAB_1483, and MAB_0540 are most commonly associated with clofazimine resistance. In addition, mutations in MAB_0416c, MAB_4099c, MAB_2613, MAB_0409, and MAB_1426 were also associated with clofazimine resistance but less frequently. Two identical mutations which are likely to be polymorphisms unrelated to clofazimine resistance were found in MAB_4605c and MAB_4323 in 13 mutants. We conclude that mutations in MAB_2299c, MAB_1483, and MAB_0540 are the major mechanisms of clofazimine resistance in *M. abscessus.* Future studies are needed to address the role of the identified mutations in clofazimine resistance in *M. abscessus.* Our findings have implications for understanding mechanisms of resistance to clofazimine and for rapid detection of clofazimine resistance in this organism.

Antimicrobial Agents and Chemotherapy

MECHANISMS OF RESISTANCE

Novel Mutations Associated with Clofazimine Resistance in *Mycobacterium abscessus*

Role of Epistasis in Amikacin, Kanamycin, Bedaquiline, and Clofazimine Resistance in Mycobacterium tuberculosis Complex / R. Vargas, L. Freshi, A. Tahseen [et al.] // Antimicrob. Agents Chemother. – 2021. – Vol. 65, N 11. - N e0116421. doi: 10.1128/AAC.01164-21. Epub 2021 Aug 30.

Antibiotic resistance among bacterial pathogens poses a major global health threat. *Mycobacterium tuberculosis* complex (MTBC) is estimated to have the highest resistance rates of any pathogen globally. Given the low growth rate and the need for a biosafety level 3 laboratory, the only realistic avenue to scale up drug susceptibility testing (DST) for this pathogen is to rely on genotypic techniques. This raises the fundamental question of whether a mutation is a reliable surrogate for phenotypic resistance or whether the presence of a second mutation can completely counteract its effect, resulting in major diagnostic errors (i.e., systematic false resistance results). To date, such epistatic interactions have only been reported for streptomycin that is now rarely used. By analyzing more than 31,000 MTBC genomes, we demonstrated that the *eis* C-14T promoter mutation, which is interrogated by several genotypic DST assays endorsed by the World Health Organization, cannot confer resistance to amikacin and kanamycin if it coincides with loss-of-function (LoF) mutations in the coding region of *eis*. To our knowledge, this represents the first definitive example of antibiotic reversion in MTBC. Moreover, we raise the possibility that *mmpR (Rv0678)* mutations are not valid markers of resistance to bedaquiline and clofazimine if these coincide with an LoF mutation in the efflux pump encoded by *mmpS5* (Rv0677c)and *mmpL5 (Rv0676c).*

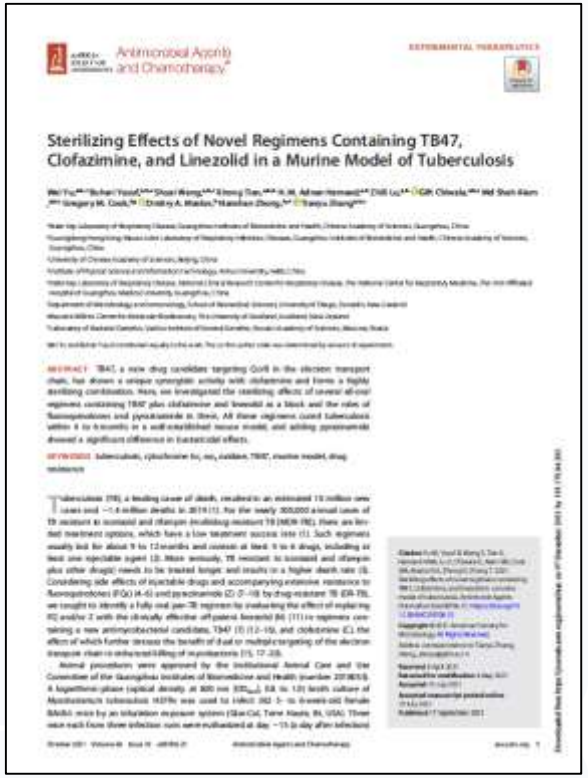

Antimicrobial Agents and Chemotherapy

MECHANISMS OF RESISTANCE

Role of Epistasis in Amikacin, Kanamycin, Bedaquiline, and Clofazimine Resistance in *Mycobacterium tuberculosis* Complex

Sterilizing Effects of Novel Regimens Containing TB47, Clofazimine, and Linezolid in a Murine Model of Tuberculosis / W. Yu, B. Yusuf, S. Wang [et al.] // Antimicrob. Agents Chemother. – 2021. – Vol. 65, N 10. – N e0070621. doi: 10.1128/AAC.00706-21. Epub 2021 Jul 19.

TB47, a new drug candidate targeting QcrB in the electron transport chain, has shown a unique synergistic activity with clofazimine and forms a highly sterilizing combination. Here, we investigated the sterilizing effects of several all-oral regimens containing TB47 plus clofazimine and linezolid as a block and the roles of fluoroquinolones and pyrazinamide in them. All these regimens cured tuberculosis within 4 to 6 months in a well-established mouse model, and adding pyrazinamide showed a significant difference in bactericidal effects.



Antimicrobial Agents and Chemotherapy

EXPERIMENTAL THERAPEUTICS

Sterilizing Effects of Novel Regimens Containing TB47, Clofazimine, and Linezolid in a Murine Model of Tuberculosis

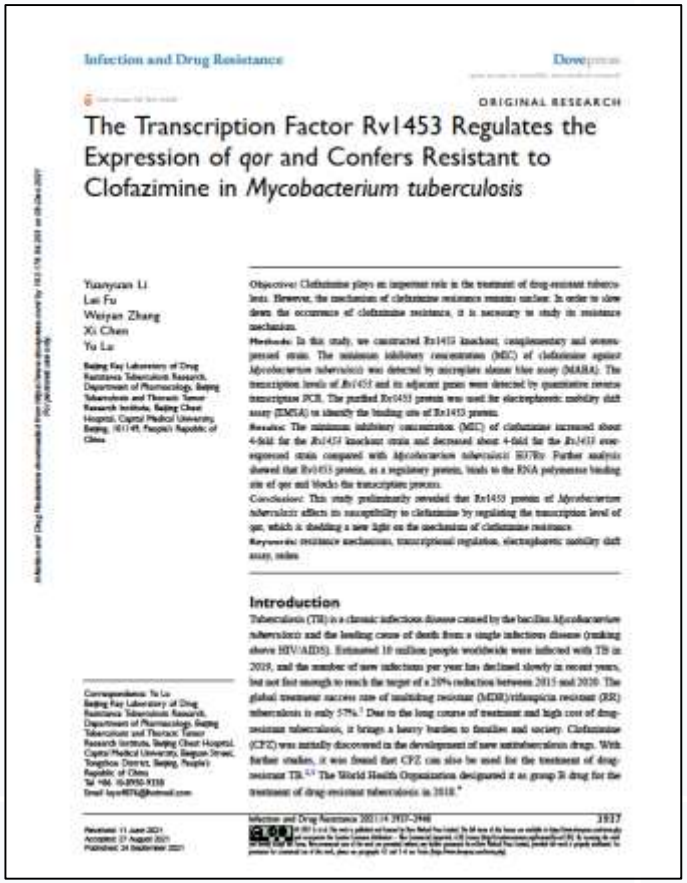
The Transcription Factor Rv1453 Regulates the Expression of qor and Confers Resistant to Clofazimine in Mycobacterium tuberculosis / Y. Li, W. Zhang, X. Chen, Y. Lu // Infect. Drug Resist. – 2021. – Vol. 14. – N 3937-3948. doi: 10.2147/IDR.S324043. eCollection 2021.

Objective: Clofazimine plays an important role in the treatment of drug-resistant tuberculosis. However, the mechanism of clofazimine resistance remains unclear. In order to slow down the occurrence of clofazimine resistance, it is necessary to study its resistance mechanism.

Methods: In this study, we constructed Rv1453 knockout, complementary and overex-pressed strain. The minimum inhibitory concentration (MIC) of clofazimine against *Mycobacterium tuberculosis* was detected by microplate alamar blue assay (MABA). The transcription levels of *Rv1453* and its adjacent genes were detected by quantitative reverse transcriptase PCR. The purified Rv1453 protein was used for electrophoretic mobility shift assay (EMSA) to identify the binding site of Rv1453 protein.

Results: The minimum inhibitory concentration (MIC) of clofazimine increased about 4-fold for the *Rv1453* knockout strain and decreased about 4-fold for the *Rv1453* over-expressed strain compared with *Mycobacterium tuberculosis* H37Rv. Further analysis showed that Rv1453 protein, as a regulatory protein, binds to the RNA polymerase binding site of qor and blocks the transcription process.

Conclusion: This study preliminarily revealed that Rv1453 protein of *Mycobacterium tuberculosis* affects its susceptibility to clofazimine by regulating the transcription level of qor, which is shedding a new light on the mechanism of clofazimine resistance.



Infection and Drug Resistance

Dovepress

ORIGINAL RESEARCH

The Transcription Factor Rv1453 Regulates the Expression of *qor* and Confers Resistant to Clofazimine in *Mycobacterium tuberculosis*

Introduction