Detection of fluoroquinolone

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Submission date: 10-Aug-2022 05:18PM (UTC+0700)
Submission ID: 1880975745
File name: late_caused_by_mutation_in_the_gyrA_gene_JKK,_SINTA_4,_2022.pdf (150.92K)
Word count: 2791
Character count: 16281

Jurnal Kedokteran dan Kesehatan: Publikasi Ilmiah Fakultas Kedokteran Universitas Sriwijaya
Volume 9, No 1. 2022/DOI: 10.32539/JKK.V9I1.16554
p-ISSN 2406-7431; e-ISSN 2614-0411

Detection of Fluoroquinolone Resistance in *Mycobacterium tuberculosis* Isolate caused by Mutation in the *gyrA* gene

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received 3 Januari 2022; accepted 10 Maret 2022

Abstrak

Tuberkulosis yang resistan terhadap obat merupakan masalah kesehatan masyarakat. TB yang resistan terhadap obat rifampisin dan isoniazid dikenal sebagai MDR-TB, sedangkan XDR-TB adalah MDR-TB yang juga resisten terhadap obat lini kedua, seperti fluoroquinolones (levofloxacin, ofloxacin, dan moxifloxacin). tuberkulosis yang resistan terhadap rifampisin (RR-TB), di mana 78 persen di antaranya menderita tuberkulosis yang resistan terhadap berbagai obat (MDR-TB) (MDR-TB). Fluoroquinolones adalah kelas antimikroba spektrum luas yang telah menjadi semakin populer dalam beberapa tahun terakhir. Fluoroquinolones memiliki aktivitas melawan Mycobacterium tuberculosis baik secara in vitro maupun in vivo. Fluoroquinolones dapat menyebabkan resistensi jika digunakan secara tidak tepat atau berlebihan. Menurut beberapa penyelidikan, mayoritas isolat M. tuberculosis yang resistan terhadap fluorokuinolon (sekitar 50-90 persen) memiliki mutasi pada gen gyrA Daerah Penentuan Resistensi Kuinolon QRDR. Namun, keterlibatan genetik dari berbagai mutasi gen gyrA pada isolat Mycobacterium TB yang resisten terhadap resistensi fluoroquinolone tetap menjadi pola mutasi gen gyrA yang tidak diketahui pada isolat Mycobacterium tuberculosis yang resisten. Pada penelitian sebelumnya, mutasi pada gen gyrA ditemukan pada kodon 90 dan 94.

Kata kunci: Fluoroquinolones, TB Resistan Obat, XDR-TB, gen gyrA

Abstract

Drug-resistant tuberculosis is a public health concern. TB that is drug-resistant to rifampin and isoniazid is known as MDR-TB, whereas XDR-TB is MDR-TB that is also resistant to second-line medicines, such as fluoroquinolones (levofloxacin, ofloxacin, and moxifloxacin). rifampin-resistant tuberculosis (RR-TB), of which 78 percent had multidrug-resistant tuberculosis (MDR-TB) (MDR-TB). Fluoroquinolones are a class of broad-spectrum antimicrobials that have become increasingly popular in recent years. Fluoroquinolones have activity against *Mycobacterium tuberculosis* both in vitro and in vivo. Fluoroquinolones might cause resistance if they are used inappropriately or excessively. According to several investigations, the majority of fluoroquinolone-resistant M. tuberculosis isolates (approximately 50-90 percent) had mutations in the *gyrA* gene QRDR Quinolone Resistance Determination Region. However, the genetic involvement of various *gyrA* gene mutations in resistant Mycobacterium TB isolates against fluoroquinolone resistance remains an unknown *gyrA* gene mutation pattern in resistant *Mycobacterium tuberculosis* isolates. In the previous investigation, mutations in the *gyrA* gene were discovered at codons 90 and 94.

Keywords: Fluoroquinolones, Drug-Resistant TB, XDR-TB, *gyrA* gene

1. Introduction

Tuberculosis is a worldwide health concern caused by the bacterium *Mycobacterium tuberculosis*, which most commonly affects the lungs. After HIV, tuberculosis is one of the top 10 causes of death worldwide (1)(2). Tuberculosis can be cured and prevented with adequate inspection and treatment (2). In 2018, 10 million people contracted tuberculosis, 1.5 million died (including 251,000 HIV-positive adults), and an estimated 1 million children were infected, with 230,000 children dying (including children with associated TB). AIDS (HIV/AIDS (3). Multidrug-resistant tuberculosis, or MDR-TB, is still a public health issue. MDR-TB is tuberculosis resistant to rifampin and isoniazid, whereas XDR-TB is MDR-TB with resistance to second-line anti-TB medications such as the fluoroquinolone group (levofloxacin, ofloxacin, and moxifloxacin), and also one of the second-line OAT injectable therapies like amikacin, kanamycin, and capreomycin (3)(4)(5)(6).

According to the WHO, 558,000 new cases of rifampin resistance, the most effective first-line treatment, have been reported, with 82 percent of those having MDR-TB(2). In 2016, the majority of projected tuberculosis cases (45 %) occurred in Southeast Asia, including Indonesia, and 25% occurred in Africa(7). Indonesia was ranked second for tuberculosis after India (8). In 2017, Indonesia had 420,994 new TB cases (statistics as of May 17, 2018). 2018 (Ministry of Health). Because fluoroquinolones were previously commonly prescribed for various infectious diseases such as respiratory, urinary, and vaginal infections, they have developed resistance as second-line therapy for MDR-TB. If fluoroquinolones are used inappropriately or in excess, they can create resistance (9)

Several studies have found that the majority of M. tuberculosis resistant fluorokuinolon isolates (about 50-90 %) have mutations in the QRDR - Quinolone Resistance Determining Region gen *gyrA* (10)(11). However, the genetic involvement of various *gyrA* gene mutations in resistant Mycobacterium TB isolates against fluoroquinolone resistance remains an unknown *gyrA* gene mutation pattern in resistant *Mycobacterium tuberculosis* isolates, which will be discussed in this review.

2. Mycobacterium tuberculosis

2.1 Definition and Characteristics

Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis* which often attacks the lungs. Transmission can be through the air when a TB patient expels droplets when sneezing or coughing. If the air is infected with tuberculosis bacteria, if it is inhaled or inhaled by a healthy person, the healthy person will be infected with TB disease.

Tuberculosis has attacked a quarter of the world's population but with a high immune system, the person does not get sick and cannot spread the disease. if a person has a low immune system then that person is more susceptible to infection with tuberculosis such as people with HIV, malnutrition, diabetes, smoking. Tuberculosis can be prevented and treated if the disease is detected early. Cough, fever, night sweats, and loss of appetite are indeed symptoms of tuberculosis. Through close contact, TB patients can infect 5-15 other people. Patients with HIV-negative TB and HIV-positive people with TB will both die if they do not receive appropriate treatment(12). *Mycobacterium tuberculosis* is a non-motile obligate aerobic, acid-fast. Basil is 2-4 um long and has a very slow generation time of between 15 and 20 hours. The mycobacterial cell wall is composed of acidic waxes, particularly mycolic acid. When a Gram stain test is performed, *Mycobacterium tuberculosis* will show a weak "Gram-positive" stain or no color at all due to the high concentration of lipids and mycolic acid in the cell walls (6). Acid-fast bacilli are bacteria that can retain their color even after being given an acid solution (13). The most common acid staining techniques are the Ziehl-Neelsen staining technique, which gives AFB bacteria a bright red color when placed on a blue background, and the auramine-rhodamine staining technique, which gives AFB bacteria a golden brown color when viewed with a fluorescent microscope.

2.2 Genome *Mycobacterium tuberculosis*

The genome of *Mycobacterium tuberculosis* is 4,411,522 base pairs long with 3,924 predicted protein-coding sequences and a relatively high G (Guanin) +C (cytosine) content of 65.6 percent. At 4.4 Mbp, *Mycobacterium tuberculosis* is one of the largest known bacterial genomes, coming in just short of *Eschericia coli*, and a distant third to *Streptomyces coelicolor* (14).*gyrA* gene is one of the important genes in *Mycobacterium tuberculosis,* encoding for DNA gyrase subunit A with locus tag in b2331 (14).

3. Drug Resistance

Mycobacterium tuberculosis has built-in drug resistance. Resistance is influenced by the existence of enzymes that can modify drugs, such as b-lactamase and aminoglycoside acetyltransferase (15). Antibiotic resistance develops (acquires) as a result of antibiotic noncompliance.

There are 5 resistant categorien (16): (1) **Monoresistance**: resistant to any of the OAT, (2) **Polyresistance**: resistant to more than one drug, other than the combination of isoniazid and rifampin, (3) **Multi-Drug Resistance (MDR):** resistant to isoniazid and rifampin, with or without other first-line drugs, (4) **Extensively Drug Resistance (XDR):** MDR TB is accompanied by resistance to one of the fluoroquinolone drugs and one of the second-line injectable OATs (capreomycin, kanamycin, and amikacin), and (5) **Rifampicin-resistant TB (RR TB)**: resistant to rifampin2.4 2nd line Anti-Tuberculosis Drug) detected using phenotypic and genotypic methods with or without resistance to other OATs (16).

3.1 Fluoroquinolone

Fluoroquinolones are effective antituberculosis medications. By boosting the level of DNA breaking caused by *gyrA*se, an important type II topoisomerase that governs DNA topology, fluoroquinolones can kill *Mycobacterium tuberculosa*, the organism that causes tuberculosis. Fluoroquinolones are broad-spectrum antibacterials that work by boosting the rate at which type II topoisomerase breaks DNA strands (17). *GyrA*se and topoisomerase IV are two types II enzymes that are found in almost every bacterial species [17]. *gyrA*se regulates the density of the bacterial chromosomal superhelix and relieves torsional stress in this species, while topoisomerase IV principally unlocks and deciphers Mycobacterium TB, the causative agent of tuberculosis, which is uncommon in that it only encodes *gyrA*se. As a result, this enzyme possesses the functional characteristics of both type II and type III topoisomerases (18).

4. *gyrA* Gene Mutation

One of the causes of MDR-TB resistance is the presence of mutations in *gyrA*. Mutations in the gene encode the DNA *gyrA*se subunit; gyr A is the most common cause of fluoroquinolone resistance in TB, reaching 90 percent (5)(18)(19)(20). The most frequent mutations associated with resistance occur in the conservation region of *gyrA*, i.e. codons 74 to 113 are known as quinolones of the resistance-determining region – Quinolone Region Drug Resistance (QRDR), as seen on figure 1 below (5).

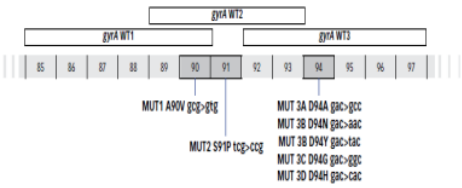

Figure 2. Specific regions for detecting fluoroquinolone mutation [23]

The main mechanism of fluoroquinolone resistance in Mycobacterium TB is *Gyr*A mutations at codons 90, 91, and 94. According to a systematic review by Mauri et al, mutations in these three codons account for 50% of fluoroquinolone resistance, whereas mutations in codon 91 of the *gyrA* gene are linked to low-grade ofloxacin resistance (15)(18) (21). A90V, D94G, and A90VD94G (double mutant) were the most prevalent mutations linked with high levels of fluoroquinolone resistance in clinical isolates of tuberculosis patients (21). This three-codon mutation can be found in 40% of ofloxacin-resistant bacteria (5).

Mutations in the gene that codes for the DNA *gyrA*se subunit A. The *gyrA* gene is tested for fluoroquinolone resistance (eg, ofloxacin or moxifloxacin). There are three wild-type gene loci in the *gyrA* gene: *gyrA* WT1, *gyrA* WT2, and *gyrA* WT3. If a mutation occurs, a band will disappear at one of the wild-type gene loci (*gyrA* WT1, *gyrA* WT2, or *gyrA* WT3) and a band will appear in one of the mutant genes (*gyrA* MUT1, MUT2, or MUT3). This results in a resistance profile that looks to be fluoroquinolone-resistant.

Several studies have shown that mutations at codon 94 in *gyrA* are associated with higher rates of fluoroquinolone (22). Based on the research of Chien et al in 2016, 55 isolates of *Mycobacterium tuberculosis* resistant to ofloxacin found isolates resistant to low-grade and high-grade MFX had a higher prevalence of mutations in *gyrA* codons 88 to 94 as well as mutations in gyrB G512R. The D94G mutation in *gyrA* and the G512R mutation in gyrB correlated with high-grade MFX resistance, whereas the D94A mutation was associated with low-grade MFX resistance (23).

Mutations at codons 88 to 94 of the *gyrA* gene are associated with OFX and MFX resistance in East Asian (Beijing), Euro-American, and Indo-Oceanic strains(19).

5. Conclusion

MDR-TB resistance can be caused by mutations in the *gyrA* gene. *gyrA* mutations at codons 90, 91, and 94 are the main mechanism of fluoroquinolone resistance in Mycobacterium TB. Mutations in the DNA *gyrA*se subunit gene. Fluoroquinolone resistance was assessed using the *gyrA* gene (ofloxacin or moxifloxacin). The *gyrA* gene has three wild-type gene loci: *gyrA* WT1, *gyrA* WT2, and *gyrA* WT3. A band will disappear at one of the wild-type gene loci (*gyrA* WT1, *gyrA* WT2, or *gyrA* WT3) and a band will appear at one of the mutant genes if a mutation occurs (*gyrA* MUT1, MUT2, or MUT3). resistant to fluoroquinolones.

References

1. Meaza A, Kebede A, Yaregal Z, Dagne Z, Moga S, Yenew B, et al. Evaluation of genotype MTBDRplus VER 2.0 line probe assay for the detection of MDR-TB in smear positive and negative sputum samples. BMC Infect Dis [Internet]. 2017 Dec 17;17(1):280. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2389-6
2. WHO, Word Health Organiztion 2018. Global tuberculosis report. 2018.
3. WHO, Word Health Organiztion 2019. Global tuberculosis report. 2019.
4. Yadav RN, Kumar Singh B, Sharma R, Chaubey J, Sinha S, Jorwal P. Comparative Performance of Line Probe Assay (Version 2) and Xpert MTB/RIF Assay for Early Diagnosis of Rifampicin-Resistant Pulmonary Tuberculosis. Tuberc Respir Dis (Seoul) [Internet]. 2021 Jul 1;84(3):237–44. Available from: http://e-trd.org/journal/view.php?doi=10.4046/trd.2020.0171
5. Bakuła Z, Napiórkowska A, Kamiński M, Augustynowicz-Kopeć E, Zwolska Z, Bielecki J, et al. Second-line anti-tuberculosis drug resistance and its genetic determinants in multidrug-resistant Mycobacterium tuberculosis clinical isolates. J Microbiol Immunol Infect [Internet]. 2016 Jun;49(3):439–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1684118215007471
6. Schlossberg D 2017. Tuberculosis And Non-Tuberculous Mycobacterial Infections. 7th ed. ASM Press. 2017;
7. WHO, Word Health Organiztion 2016. Global Tuberculosis Report.
8. WHO, Word Health Organiztion 2020. Global Tuberculosis Report.
9. Singh P, Jain A, Dixit P, Prakash S, Jaiswal I, Venkatesh V SM 2015. Prevalence of GyrA and B Gene Mutations In Fluoroquinolone-Resistant and -Sensitive Clinical Isolates of Mycobacterium tuberculosis and Their Relationship With MIC of Ofloksasin. J Antibiot No 68, pp 63–66.
10. Yin X, Yu Z. Mutation characterization of gyrA and gyrB genes in levofloxacin-resistant Mycobacterium tuberculosis clinical isolates from Guangdong Province in China. J Infect [Internet]. 2010 Aug;61(2):150–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0163445310001325
11. Brossier F, Veziris N, Aubry A, Jarlier V, Sougakoff W. Detection by GenoType MTBDR sl Test of Complex Mechanisms of Resistance to Second-Line Drugs and Ethambutol in Multidrug-Resistant Mycobacterium tuberculosis Complex Isolates. J Clin Microbiol [Internet]. 2010 May;48(5):1683–9. Available from: https://journals.asm.org/doi/10.1128/JCM.01947-09
12. WHO 2021. Global Tuberculosis

Report. World Health Organization.
13. Tille PM 2017. Bailey & Scott's: Diagnostic Microbiology. 14th ed. Missouri: Elsevier.
14. Coll F, Preston M, Guerra-Assunção JA, Hill-Cawthorn G, Harris D, Perdigão J, et al. PolyTB: A genomic variation map for Mycobacterium tuberculosis. Tuberculosis [Internet]. 2014 May;94(3):346–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1472979214203428
15. Nguyen L. Antibiotic resistance mechanisms in M. tuberculosis: an update. Arch Toxicol [Internet]. 2016 Jul 9;90(7):1585–604. Available from: http://link.springer.com/10.1007/s00204-016-1727-6
16. Kemenkes RI 2018. Tuberculosis. Pusat Data Dan Informasi Kemenkes RI.
17. Aldred KJ, Kerns RJ, Osheroff N. Mechanism of Quinolone Action and Resistance. Biochemistry [Internet]. 2014 Mar 18;53(10):1565–74. Available from: https://pubs.acs.org/doi/10.1021/bi5000564
18. Farhat MR, Jacobson KR, Franke MF, Kaur D, Sloutsky A, Mitnick CD, et al. Gyrase Mutations Are Associated with Variable Levels of Fluoroquinolone Resistance in Mycobacterium tuberculosis. Carroll KC, editor. J Clin Microbiol [Internet]. 2016 Mar;54(3):727–33. Available from: https://journals.asm.org/doi/10.1128/JCM.02775-15
19. Chien J-Y, Chiu W-Y, Chien S-T, Chiang C-J, Yu C-J, Hsueh P-R. Mutations in gyrA and gyrB among Fluoroquinolone- and Multidrug-Resistant Mycobacterium tuberculosis Isolates. Antimicrob Agents Chemother [Internet]. 2016 Apr;60(4):2090–6. Available from: https://journals.asm.org/doi/10.1128/AAC.01049-15
20. Salah Eldin A, Mostafa NM, Mostafa SI. Detection of fluoroquinolone resistance in Mycobacterium tuberculosis clinical isolates as determined by gyrA/B gene mutation by using PCR technique. Egypt J Chest Dis Tuberc [Internet]. 2012 Oct;61(4):349–53. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0422763812000465
21. Pandey B, Grover S, Tyagi C, Goyal S, Jamal S, Singh A, et al. Dynamics of fluoroquinolones induced resistance in DNA gyrase of Mycobacterium tuberculosis. J Biomol Struct Dyn [Internet]. 2018 Jan 25;36(2):362–75. Available from: https://www.tandfonline.com/doi/full/10.1080/07391102.2016.1277784
22. Li D, Hu Y, Werngern J, Mansjo M, Zheng X, Drobnieewski, Hoffener S XB 2016. Emergence and genetic characteristic of pyrazinamide resistant tuberculosis in China, a multi-center study. Antimicrob Agents Chemother 60 5159-5166.
23. Global Laboratory Initiative. 2018. Line probe assays for drug-resistant tuberculosis detection Interpretation and reporting guide for laboratory staff and clinicians. Global TB Programme World Health Organization Geneva, Switzerland.

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