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Treatment Duration and Drug Regimen Correlation with Side Effects Incidence in Drug-Resistant Tuberculosis (DR-TB) Patients at Pulmonary Hospital

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ABSTRACT: The bacteria *Mycobacterium tuberculosis* causes Drug-Resistant Tuberculosis (DR-TB). Excessive use of drugs can result in drug resistance with various side effects. This study aimed to analyze the correlation between the treatment duration and drug regimen with the side effects incidence in DR-TB Patients at Pulmonary Hospital Dr. M. Goenawan Partoidigdo (RSPG) Bogor. This is an observational study with a cross-sectional design. Subjects were selected with purposive sampling methods based on inclusion and exclusion criteria. The research showed that DR-TB patients were mostly male (50.2%) with productive age (46.1%). The most common DR-TB treatment experienced by patients in the advanced phase, generally for 9-24 months (75.3%), and the type of drug side effect most experienced was gastrointestinal disorders, that is nausea (55.1%). The use of standard conventional drug regimens mostly in Z, E, Eto, Km, Lfx, Cs (Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Levofloxacin, Cycloserine) of 51.4%. The chi-square analysis showed no significant correlation between the treatment duration and the incidence of side effects. At the same time, there was a meaningful correlation between the drug regimen (short-term, long-term, and conventional standard regimen) and the side effects incidence. The suspected drugs causing gastrointestinal side effects were pyrazinamide, ethambutol, ethionamide, and levofloxacin. The side effects of arthritic arthralgia were suspected to be caused by pyrazinamide, ethionamide, and levofloxacin.

Keywords: **DR-TB patients; anti-tuberculosis drugs; side effects incidence; treatment duration; drug regimen.**

Introduction

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. This health problem is the most dangerous in the world. The transmission source is tiny droplets of inhaled phlegm expelled, including in Indonesia. The fact that many cases are still found, which is constantly increasing yearly. According to the national report [1], the number of new tuberculosis cases in Indonesia is 420.994. The province with the highest prevalence of Tuberculosis in Indonesia, West Java, ranked 3rd, and Bogor district is ranked 10th with 190 cases in 100.000 population. It has experienced an increase from the previous year of 166 points in 100.000 residents originating from new patients, and 20% failed from the last treatment [2].

The increase in cases could be due to drug resistance. Tuberculosis is a severe problem because the implementation of treatment is challenging to carry out, and the period is longer, the treatment success rate is only 57% so more people experienced death in 2017, it was estimated that around 18.5% experienced deaths caused by DR-TB cases. DR-TB occurs if infected with Mycobacterium tuberculosis bacteria with resistance to various of the most effective first-line Anti-Tuberculosis Drugs (ATDs), with a minimum of two ATDs of isoniazid and rifampicin [3].

Clinical management of resistant tuberculosis is more complicated than non-resistant tuberculosis because the body has immunity to ATDs. Reviono et al. [4] stated that the most side effects were digestive disorders,

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namely nausea and vomiting 79.8%, joint pain 78.9%, and kidney disorders. Back up drugs are accompanied by many undesirable drug reactions, requiring changes in the treatment plan. Based on these conditions, researchers will analyze the problem of treatment duration and the incidence of side effects in DR-TB patients because prevalence continues to increase, it is necessary to analyze treatment to reduce the incidence of undesirable events. This study explores the correlation between the treatment duration and drug regimen with the incidence of the side effects in DR-TB patients at pulmonary hospital Dr. M. Goenawan Partoidigdo (RSPG) Bogor.

Method

Study Design and Sampling Technique

The study used an observational, cross-sectional design to analyze the correlation between the treatment duration and drug regimen with the incidence of side effects in DR-TB Patients at Pulmonary Hospital Dr. M. Goenawan Partoidigdo (RSPG) Bogor. Data was collected retrospectively using patient medical record data from 2018 - 2020. Sampling was carried out by consideration or purposive. Purposive sampling is a technique that meets inclusion and exclusion criteria. This study has been approved by a research ethics committee No.078/UN6. KEP/EC/2021 (Figure 1).

Inclusion and Exclusion Criteria

The inclusion criteria in this study were: 1) Patients diagnosed with DR-TB, 2) Patients undergoing long-term and short-term treatment, 3) Patients undergoing outpatient treatment at Pulmonary Hospital Dr. M. Goenawan Partowidigdo, 4) Patients whose treatment data is complete to assess side effects, 5) Patients undergoing treatment from the start of treatment 0 months. The exclusion criteria in this study were patients whose medical record data was damaged/ incomplete.

Data Analysis

The data were analyzed using the univariate analysis and will be continued with bivariate analysis. All data is processed using the statistics program and then presented in percentage form in a frequency distribution table. Univariate statistical analysis tests were conducted to examine the treatment duration, incidence of side effects, age, and gender. The bivariate analysis with a chi-square test to see the correlation between treatment duration and side effects incidence and the correlation between drug regimen and side effects incidence.

Results and Discussion

Two hundred forty-three samples met the inclusion criteria. Patient characteristics based on gender were 122 males (50.2%) and 121 females (49.8%). This is commensurate with the previous research that men's distribution was more than women's (63.5%) [5]. The prevalence of Tuberculosis tends to occur in men rather than women [1]. This is associated with men's activities having a heavier workload, lack of rest, or an unhealthy lifestyle such as drinking alcohol and smoking [6]. Based on age, it was found that the youngest was 14 years old, and the oldest was 79 years old. Most of this study's samples were 35-54 years old (46.1%). At this age, they generally have highly productive activities, namely leaving the house, especially for daily work, so they do not take medication regularly and regularly.

Table 1. DR-TB Regimen

Regimen Type	DR-TB Patients					N
	2 drugs	3 drugs	4 drugs	5 drugs	6 drugs	
Short-term						
Bdq, Lfx, Cfz, H, Z, E, Eto	0	3	14	56	2	75 (30.9%)
Long-term						
Bdq, Lfx/Mfx, Lzd, Cfz, Cs	0	5	14	24	0	43 (17.7%)
Conventional Standard						
Z, E, Eto, Km, Lfx, Cs	1	0	3	46	75	125 (51.4%)

Notes :
Bdq (Bedaquiline); Lfx (Levofloxacin); Cfz (Clofazimine); H (Isoniazid); Z (Pyrazinamide); E (Ethambutol); Eto (Ethionamide); Mfx (Moxifloxacin); Km (Kanamycin); Cs (cycloserine)

The length of treatment variable was dominated by 9-24 months with 183 peoples (75.3%). The frequency of treatment duration was determined based on the regimen used and the patient's condition, who is resistant to fluoroquinolones [7]. This is in line with research conducted in Makassar Regional Hospital that the highest length of treatment undergone by patients was the advanced phase, which had been treated for 9-12 months and 13-16 months [8]. According to other research, with successful treatment, the patient will recover if he completes the planned duration of therapy, has clinical evidence of healing, and has a sputum sample cultured negative [9]. According to Kemenkes, the treatment duration for Drug-Resistant Tuberculosis is that the short-term treatment regimen is 9-11 months, and the long-term regimen is 18-24 months [3].

The characteristics of drug regimen as shown in Table 1, the most widely used administration is the conventional standard regimen, namely Z, E, Eto, Km, Lfx, Cs (Pyrazinamide, Ethambutol, Etionamid, Kanamycin, Levofloxacin, Cycloserine) of 125 peoples (51.4%), the second is in the combination of short-term regimens namely Bdq, Lfx, Cfz, H, Z, E, Eto (Bedaquiline, Levofloxacin, Clofazimin, Isoniazid, Pyrazinamide, Ethambutol, Etionamid) of 75 peoples (30.9%), and long-term combinations namely Bdq, Lfx/Mfx, Lzd, Cfz, Cs (Bedaquiline, Levofloxacin/Moxifloxacin, Linezolid, Clofazimine, Cycloserine) of 43 peoples (17.7%). According to [10] the short-term regimen Bdq, Lfx/Mfx, Lzd, Cfz, Cs (Bedaquiline, Levofloxacin/Moxifloxacin, Linezolid, Clofazimine, Cycloserine) recommended by the World Health Organization for DR-TB and drug susceptibility-TB, during the Covid-19 pandemic will provide relief patient burden and simplify the patient's health care system. Research conducted in India by Gupta said that the treatment success rate was using four, five, or six drugs [11].

Adverse drug reaction (ADR, or adverse drug effect) is a broad term referring to unwanted, uncomfortable, or dangerous effects that drugs (including medications) may have. Adverse drug reactions are usually classified as mild, moderate, severe, or lethal [12]. The side effects were not predominantly reported in the medical records, and the complaints were included in the favorable side

Table 2. Side Effects of DR-TB Drugs

Side effects	RSPG Cisarua N = 243	
	N	%
Gastrointestinal		
Nauseous	134	55.1
Vomit	124	51.0
Diarrhea	4	1.6
Musculoskeletal		
Increased Uric Acid	86	35.4
Joint pain	60	24.7
Psychiatry		
Sleep disorders	21	8.6
Worried	6	2.5
Sensory		
Hearing disorders	18	7.4
Skin		
Itchy	14	5.8
Systemic		
Tachycardia	9	3.7
Vertigo	7	2.9
Chest pain	6	2.5

effect category. As shown in Table 2, the most frequent mild side effects were 214 peoples (88.1%), and the least frequent were 29 peoples (11.9%) with serious side effects. According to the Indonesian Ministry of Health's DR-TB management guide [3], the side effects that arise can still be handled by the patient and surrounding medical personnel so they are still included in the category of mild side effects, namely dizziness/ headache, muscle and bone pain, tingling, pain at the injection site, nausea, vomiting, hyperuricemia, itching, diarrhea, vertigo, anxiety, sleep disorders. Side effects that patients and medical personnel cannot handle include serious side effects, namely shortness of breath, chest pain, palpitations, weakness and lethargy, hallucinations, and reduced hearing [13]. This aligns with research conducted [14] that mild side effects often occur.

Table 2 showed that the side effects of gastrointestinal disorders were nausea (134 peoples or 55.1%) and vomiting (124 peoples or 51.0%). Most of them experience gastrointestinal disorders (nausea and vomiting) after taking the DR-TB drugs. According to the Indonesian Ministry of Health's DR-TB management guide [3], the cause of gastrointestinal side effects is the use of ethionamide, prothionamide, clofazimine, isoniazid, ethambutol, pyrazinamide, levofloxacin, moxifloxacin, linezolid, bedaquiline, delamanid, and p-amino salicylate. The side effects of increased uric acid and joint pain were found in 86 peoples (35.4%) and 60 peoples (24.7%). Elevated uric acid is a common clinical condition defined as a serum uric acid level higher than the average value of >6 mg/dl. Based on the literature on the side effects of increased uric acid caused by the drugs Pyrazinamide, Levofloxacin, and Ethambutol [3]. This symptom was also found in DR-TB patients in this study. In hospital findings, some patients combined pyrazinamide with ethambutol alone. This aligns with research conducted in India that increased uric acid was due to using pyrazinamide with a sample of 196 patients, and 56 peoples (28.57%) experienced increased uric acid laboratory results [15]. In non-gouty patients, the increase in uric acid results is thought to be caused by pyrazinamide and ethambutol induction, which leads to arthralgia. Pyrazinoic acid metabolites are responsible for the mechanism of increasing uric acid by carrying pyrazinoic acid, the primary metabolite of pyrazinamide, which is further oxidized by xanthine oxidase by inhibiting renal tubular uric acid secretion [16]. Another undesirable effect was joint pain in 60 peoples (24.7%). In this pain finding, there are many types other than joint pain. This joint pain is thought to be due to the use of bedaquiline and pyrazinamide in the guidelines for short-term (bedaquiline and pyrazinamide) joint pain.

Side effects started to occur on the 2nd day (first month) and months of treatment after taking various types of drugs. The analysis results showed no correlation between the length of treatment and the side effects of the drug because the value obtained was a p-value of 0.174 (>0.05). These results are from other research conducted in Bali by Pratiwi et al. (2016), showing no correlation between length of treatment and drug side effects, showing a p-value of 0.515. The research results show no connection between the size of treatment and drug side effects in DR-TB patients. This occurs due to various factors; it is suspected that the patient did not report his complaint to the medical staff who handled him, so it was not recorded in the medical record report [17].

According to the World Health Organization [13], as many as 80.6% of short-term regimens (9-12 months) are more beneficial for successful treatment with more prominent results than long-term regimens (24 months), so drug side effects result from drug side effects in months towards the end of therapy the distribution and frequency of patients decreased. This was stated by Dalcolmo [18] that using short-term regimens is not recommended and is not allowed to work. If you use too much medication in the long term, you will likely quickly experience side effects from the drug [19]. These results show significant results, with a p-value of 0.042 (<0.05). In this case, a substantial correlation exists between regimen administration and drug side effects. This research conducted by Malcolm [18] that there was a correlation between the type of regimen and side effect status; the p-value was found to be 0.054. In this study, the conventional standard regimen Z, E, Eto, Km, Lfx, Cs (Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Levofloxacin, Cycloserine) was more frequently used. According to the Indonesian Ministry of Health [3], pyrazinamide is suspected of causing gastrointestinal side effects, liver function abnormalities, and arthritic arthralgia. The drug ethambutol is thought to cause side effects, namely gastrointestinal and visual disturbances. Ethionamide drugs can produce side effects such as teratogenic pain, depression, gastrointestinal, liver function disorders, and arthritic arthralgia. Side effect of kanamycin is kidney function abnormalities. Levofloxacin can cause electrolyte disturbances, kidney function disorders, liver function disorders, depression, sleep disorders, gastrointestinal disorders, arthritis, arthralgia, and pain. Cycloserine causes drug side effects, such as depression, sleep disorders, and seizures. Hepatic side effects are more common when using bedaquiline and delaminate with thiazolidinedione and acarbose.

KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN
UNIVERSITAS PADJADJARAN
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Amandemen dari persetujuan etik nomor : 210/UN6.KEP/EC/2021
Amendment of ethical approved number

No.Reg.: 0221020175

PERSETUJUAN ETIK
ETHICAL APPROVAL
Nomor: 078/UN6.KEP/EC/2021

Komisi Etik Penelitian Universitas Padjadjaran Bandung, dalam upaya melindungi hak asasi dan kesejahteraan subjek penelitian serta menjamin bahwa penelitian yang menggunakan formulir survey/registrasi/surveilens/ Epidemiologi/Humaniora/Sosial Budaya/Bahan Biologi Tersimpan/Sel Punca dan non klinis lainnya berjalan dengan memperhatikan implikasi etik, hukum, sosial dan non klinis lainnya yang berlaku, telah mengkaji dengan teliti proposal penelitian berjudul:

The Research Ethics Committee Universitas Padjadjaran Bandung, in order to protect the rights and welfare of the research subject, and to guaranty that the research using survey questionnaire/registry/surveillance/ epidemiology/humaniora/social-cultural/archived biological materials/stem cell/other non clinical materials, will carried out according to ethical, legal, social implications and other applicable regulations, has been throughly reviewed the proposal entitled:

"ANALISIS HUBUNGAN LAMA PENGOBATAN DENGAN KEJADIAN EFEK SAMPING PADA PASIEN *MULTI DRUG RESISTANT* (*MDR*) TUBERKULOSIS DI RS PARU DR. M. GOENAWAN PARTOWIDIGDO CISARUA"

Nama Peneliti Utama *Principal Researcher*	:	Gita Iftitah Renitia
Pembimbing/Peneliti Lain *Supervisor/Other Researcher*	:	Apt., Lusi Indriani, M.Farm Apt., Lusi Agus Setiani, M.Farm
Nama Institusi *Institution*	:	Program Sarjana Program Studi Farmasi Fakultas Matematika dan Ilmu Pengetahuan Alam Universitas Pakuan

proposal tersebut dapat disetujui pelaksanaannya.
hereby declared that the proposal approved.

Ditetapkan di : Bandung
Specified in
Tanggal : 02-09-2021
Date

Ketua,
Chairman,

Nur Atik, dr, M.Kes., PhD
NIP. 19811010 200801 1 019

Keterangan/notes:
Keterangan/notes:
Persetujuan etik ini berlaku sampai 19 Maret 2022
This ethical clearance is effective until 19 March 2022
Pada akhir penelitian, laporan pelaksanaan penelitian harus diserahkan ke Komisi Etik Penelitian.
In the end of the research, progress and final summary report should be submitted to the Research Ethics Committee.
Jika ada perubahan atau penyimpangan protokol dan/atau perpanjangan penelitian, harus mengajukan kembali permohonan kajian etik penelitian.
If there be any protocol modification or deviation and/or extension of the study, the Principal Investigator is required to resubmit the protocol for approval.
Jika ada kejadian serius yang tidak diinginkan (KTD) harus segera dilaporkan ke Komisi Etik Penelitian.
If there are Serious Adverse Events (SAE) should be immediately reported to the Research Ethics Committee

Figure 1. Ethical Clearance

According to Septiyani [20], mild side effects can still be tolerated by the body. A drug in the body will also affect the effectiveness of its action against the side effects it causes. In this study, it can be interpreted that the type of drug regimen used affects the resulting side effects. However, DR-TB drugs are still safe to use because the administration of the drug has been considered according to indications, namely by using the medicine according to clinical needs seen from the diagnosis. The suitability of the type of drug has been determined by various aspects, namely age and appropriateness of dosage based on body weight [21].

The limitation of this research is that it was carried out retrospectively by looking at medical records and laboratory results, so the level of accuracy cannot be ascertained if it is indeed a side effect of the drug. However, this research can be used as a theoretical basis regarding the profile of drug side effects experienced by patients to monitor further drug side effects.

Conclusion

The research showed that DR-TB patients were mostly male (50.2%) with productive age (46.1%). The most common DR-TB treatment experienced by patients in the advanced phase, generally for 9-24 months (75.3%), and the type of drug side effect most experienced was gastrointestinal disorders, that is nausea (55.1%). The use of standard conventional drug regimens mostly in Z, E, Eto, Km, Lfx, Cs (Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Levofloxacin, Cycloserine) of 51.4%. The chi-square analysis results showed no significant correlation between the treatment duration and incidence of side effects. At the same time, there was a meaningful correlation between the drug regimen (short-term, long-term, and conventional standard regimen) and the side effects incidence. The suspected drugs causing gastrointestinal side effects were pyrazinamide, ethambutol, ethionamide, and levofloxacin. The side effects of arthritic arthralgia were suspected to be caused by pyrazinamide, ethionamide, and levofloxacin.

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