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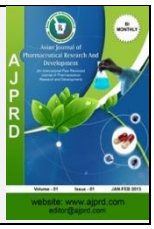

Open Access Research Article

Evaluation of Potential Drug Side Effects in Multidrug-Resistant Tuberculosis Patients who have been Diagnosed by Genexpert Method

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A B S T R A C T

Objective: to evaluation potential drug side effects in multidrug-resistant tuberculosis patients who have been diagnosed by genexpert method

Design: this research used a descriptive analysis research design. The population used in this study were MDR-TB patients at the DOTS TB and MDR TB Poly in RSUP Haji Adam Malik Medan in 2017-2019, the research sample obtained was 100 patients and data collection used a cross sectional approach.

Interventions: the intervened variable were therapeutic regimen, used of additional drugs and duration of therapy

Main outcome measures: the main measurement in this study was therapeutic side effects

Results: the results showed that treatment of MDR-TB patients mostly used the standard combination regimen, namely Km-Lfx-Eto-Cs-Z- (H) - (E) as much as 35%. Side effect found was nausea at 20.55%. The use of additional vitamin B6 drugs in MDR-TB patients was 92% because treatment using kanamycin, etionamide, levofloxacin and cycloserine had side effects of peripheral neuropathy. Of the length of treatment that was still undergoing treatment in 2019, the highest number was 59%.

Conclusion: it could be concluded the most common side effect found in the average number was nausea at 20.55% and peripheral neuropathy.

Keywords: Side effect, Multidrug-Resistant, Tuberculosis, Genexpert

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INTRODUCTION

Tuberculosis (TB) is a direct infectious disease caused by the TB germ (Mycobacterium tuberculosis) (Ministry of Health, 2011). The incidence of tuberculosis (TB) in the world is still relatively high and a serious health problem. The three countries with the most TB cases are India, China, and Indonesia, each contributing 23%, 10% and 10% of all TB cases in the world. Tuberculosis based on its location can be divided into two, namely pulmonary tuberculosis and extrapulmonary tuberculosis. Extrapulmonary tuberculosis is TB that attacks organs other than the lungs, such as the central nervous system (CNS). Currently, various methods have been developed to diagnose TB, ranging from modification of bacterial culture (MGIT, MODS), modification of staining (modified Ziehl-Neelsen, Auramine) to DNA amplification-based examinations using the polymerase chain reaction (PCR) method such as the Xpert MTB / RIF (GeneXpert). The GeneXpert examination is a real-time PCR method that can detect Mycobacterium tuberculosis as well as perform a rifampin resistance test (RIF). GeneXpert has several advantages compared to conventional PCR, namely that it can be used outside a laboratory environment because it uses a closed-cartridge based system and does not have to be done by users with special skills[1].

One of the factors of the unsuccessfulness of TB treatment includes incomplete treatment of TB patients and patient non-compliance with medication, regimens, dosages, and how to use drugs that are not correct, interrupted availability of OAT, and low quality of drugs. Patients undergoing treatment often experience difficult conditions and situations and severe challenges include long-term treatment, side effects from drugs and discrimination from the environment. TB patients who do not get complete information about TB and no counseling will affect patient adherence to TB treatment. This has an impact on increasing the risk of OAT resistance, including: Monoresistance, Polyresistance,

Multiple-Drug Resistance (MDR), Extensively-Drug Resistance (XDR), and Total Drug Resistance (Total DR)[2].
Another factor causing treatment failure that increases the risk of resistance is the side effects of treatment. All OATs used in the treatment of TB patients have the possibility of developing mild, moderate and severe side effects. If a side effect of treatment appears, the patient will likely stop treatment unilaterally without notifying it is quite large[3]. This is due to a lack of awareness for sufferers of their disease so that providing counseling and education information is very important so that patients can understand about the side effects that will occur during treatment[4].
Based on the above background, the authors are interested in conducting research on the potential side effects of drugs in MDR TB patients who have been diagnosed with the Genexpert method. The purpose of this study was to see the possible side effects of drug use in MDR TB patients. This study will determine the success of treatment in MDR TB patients who have been diagnosed with the Genexpert method by looking at the potential side effects of treatment.

MATERIALS AND METHODS

Research Place
The research was conducted at RSUP Haji Adam Malik Medan

Research time
The research was conducted in 2017-2019.

Population
The population used in this study were MDR-TB patients who had been diagnosed with the GeneXpert method at the DOTS TB and MDR TB Polyclinic at RSUP Haji Adam Malik Medan. Population is a generalization area consisting of objects / subjects that have certain qualities and characteristics that the researcher determines to study and then draw conclusions[5].

Sample
The sample used in this study were outpatient MDR-TB patients who had been diagnosed with the GeneXpert method who met the inclusion criteria at the DOTS TB and MDR TB Poli in RSUP Haji Adam Malik Medan.

Tools
Research tools in the form of data collection sheets, stationery and SPSS data processing applications.

Material
This research material uses patient medical records

Inclusion Criteria
Inclusion criteria are criteria in which research subjects qualify as samples[6].
Included in the inclusion criteria are:
a. Outpatient MDR-TB patients who were diagnosed using the GeneXpert tool in 2017 – 2019
b. Outpatient MDR-TB patients who have been diagnosed with the GeneXpert method with all genders and ages in 2017 – 2019
c. Outpatient MDR-TB patients who have been diagnosed with the GeneXpert method who have complete medical record data in 2017 – 2019.

Exclusion Criteria
Exclusion criteria are criteria in which the research subject cannot qualify as a research sample[6].
Included in the exclusion criteria were:
1. MDR-TB patients who do not have complete medical record data
2. Inpatient MDR-TB patient
3. Outpatient MDR-TB patients who were treated outside the year 2017 – 2019

RESULT AND DISCUSSION

Treatment
Treatment of MDR-TB patients mostly uses a standard combination regimen, namely Km-Lfx-Eto-Cs-Z- (H) - (E) as much as 35 (35%), with a Short Therapy Regimen namely Km-Mfx-Eto-Cfz-Z - (H) - (E) as much as 32 (32%), with an alloy of Km-Eto-Cs-PAS-Z- (E) -Bdq as much as 14 (14%), alloy Lfx-Eto-Cs-PAS-Z- (E) -Bdq as much as 7 (7%), alloy Km-Lfx- Cs-Z- (E) -BdQ-Lnz and alloy Cm-Mfx-Eto-Cs-PAS-Z- (E) - (H) respectively - 4 (4%) each, 2 (2%) Km-Lfx-PAS-Z- (E) -BdQ-Lnz alloys, Bdq-Lfx-Cfz-E-Lnz (individual 1) and Km-Lfx alloys -Cs-Lnz (individual 2) 1 (1%) each.

Treatment of resistant TB given to patients is adjusted to the type of resistance they suffer and the side effects that arise in the initial treatment, which refer to the Management Guidelines for Drug-Resistant Tuberculosis Control (MPTRO). Treatment for MDR-TB patients who have no side effects to the treatment given is given a standard OAT alloy. There are two kinds of standard OAT alloys, first, conventional standard OAT alloys with the Km-Lfx-Eto-Cs-Z- (H) - (E) regimen for 22-24 months where Km usage is only for 8-12 months (Monday-Friday). Second, the combination of short-term OAT / Short Therapy Regimen (STR) with the Km-Mfx-Eto-Cfz-Z- (H) - (E) regimen for 9-11 months where the use of Km is only for 4-6 months (Monday- week)[7]. The description of MDR-TB treatment in RSUP Haji Adam Malik Medan based on treatment showed in Fig 1.

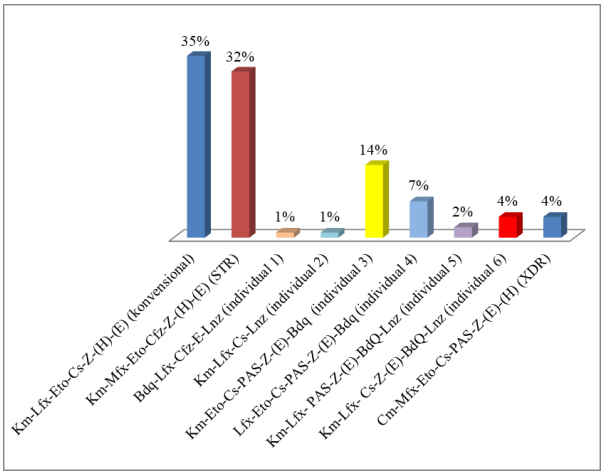

Figure.1 Frequency distribution by treatment

Information :
R: Rifampin Eto: Etionamid
Lfx: Levofloxasin H: Isoniazid
Cs: Cycloserin E: Ethambutol
Mfx: Moxifloxacin S: Streptomycin
Bdq: Bedaquilin Km: Kanamycin
Lnz: Linezolid Am: Amikasin
Cfz: Clofazimin Ofx: Ofloxasin
PAS: Para Amino Salicylate

Side Effects

In MDR-TB treatment, many side effects were found in patients who were suspected of being caused by OAT during the treatment period. In this study, the most common side effects found in the average number were nausea as much as 20.55 (20.55%), dizziness 11.22 (11.22%) vomiting 7.5 (7.5%), joint pain. 7.05 (7.05%), weakness 6.27 (6.27%), decreased hearing 5.72 (5.72%), chest pain 4.83 (4.83%), ringing ears 3.94 (3.94%), numbness 2.72 (2.72%), insomnia 1.66 (1.66%), hallucinations 1.05 (1.05%), itching 0.5 (0.5%), decreased vision 0.27 (0.27%), skin flushing and depression had the same results, namely 0.22 (0.22%) and 0.11 (0.11%) heart palpitations. OATs used for MDR-TB treatment have the possibility of mild, moderate, and severe side effects. The side effects that arise can affect the success of MDR-TB treatment so that monitoring of side effects during treatment is necessary[8].

Side effects that are often experienced by patients are nausea and vomiting which is thought to be caused by ethionamide, Para Amino Salicylate, pyrazinamide, ethambutol, isoniazid and levofloxacin[8]. These side effects mostly occur in the first month of treatment. If the nausea and vomiting are mild, then treatment is continued. If dehydrated give IV fluids. If symptoms develop after ingestion of ethionamide, stop all treatment for 1 week and restart treatment with the test dose. Continuous vomiting needs to be checked for liver function, potassium levels and creatinine levels[8].

The side effects of dizziness (vertigo) are thought to be caused by administration of kanamycin, capreomycin and ethionamide. To relieve it, it is necessary to give betahistine anti-vertigo and if possible give an injection of OAT 1 hour after oral OAT were given[8].

The side effect of joint pain is thought to be caused by pyrazinamide and levofloxacin, which can raise uric acid levels. MDR-TB treatment can be continued and its effect can be reduced with NSAIDs or can also be given allopurinol. The side effect of insomnia is thought to be caused by levofloxacin and moxifloxacin. To reduce the effect, give floroquinolone OAT in the morning away from bedtime. The side effect of ringing in the ears is thought to be caused by kanamycin and capreomycin. Before it gets worse, it is necessary to evaluate and stop using kanamycin if necessary. The side effect of hallucinations is thought to be caused by cycloserine. Do not leave the patient alone and can also stop giving the OAT suspected of being the cause. Anti-psychotic drugs and counseling can also be given. If the condition is resolved, treatment can be continued with anti-psychotic drugs[8].

Side effects of numbness are thought to be caused by cycloserine, kanamycin, etionamide and levofloxacin. If you experience this effect, treatment can be continued by increasing the dose of pyridoxine. If the effect is getting worse, cycloserine can be replaced with PAS. Side effects of itching and redness are thought to be caused by pyrazinamide, ethambutol, ethionamide, PAS, cycloserine and capreomycin. Treatment can be continued with the provision of antihistamines and if the effect is getting worse, injectable corticosteroids can be given[7].

Additional Drugs

Additional drugs using vitamin B6 as much as 92 (92%), allopurinol 23 (23%), novorapid pen 17 (17%), Lantus pen 15 (15%), alprazolam 0.5mg 13 (13%), levemir pen 11 (11 %), domperidone 10 mg 10 (10%), apidra pen 9 (9%), omeprazole 20 mg 8 (8%), sucralfate syrup and risperidone 2 mg each 6 (6%), betahistine 6 mg and THP respectively. 5 (5%), KSR 600 mg and cetirizin 10 mg each 4 (4%), amlodipine 10 mg 3 (3%), metoclopramide 2 (2%), micardis 40 mg and merlopam 2 mg each 1 (1%). The use of additional vitamin B6 drugs in MDR-TB patients because treatment using kanamycin, etionamide, levofloxacin and cycloserine has side effects of peripheral neuropathy[8].

Novorapid, lantus, levemir and apidra are insulin preparations used to control blood sugar in diabetes mellitus (DM). Diabetes is often accompanied by TB because in diabetic patients there is a decrease in the immune system so that it is very easy to develop other diseases, one of which is tuberculosis, so that treatment takes longer. The use of hypoglycemic drugs can interact with several OAT regimens, so that the most effective DM drug used is insulin[9].

The side effects of depression are thought to be caused by cycloserine, levofloxacin, and ethionamide. For depressed patients, do counseling and if necessary anti-depressants can be given. The side effects of hearing loss are thought to be caused by Kanamycin and cycloserine. If hearing loss occurs, the patient needs to be checked weekly to evaluate the hearing loss and discontinue administration of kanamycin if necessary. The side effect of decreased vision is thought to be due to ethambutol. Although the symptoms

are mild, its use must be stopped and other treatments are continued[8].

The additional drug allopurinol is used because of the side effects of joint pain that are thought to be caused by pyrazinamide and levofloxacin. Amlodipine 10 mg and mycardis 40 mg are used in patients who have a history of hypertension. Cetirizine is used as an adjunct drug in side effects of itching itching caused by pyrazinamide, ethambutol, etionamide, PAS, cycloserine and capreomycin[8].

The additional drug betahistine mesylate 6 mg was used because of the side effects of dizziness thought to be caused by kanamycin, capreomycin and ethionamide. Domperidone 10 mg and metoclopramide 10 mg were used because of the side effects of nausea and vomiting that were thought to be caused by ethionamide, PAS, pyrazinamide, ethambutol and levofloxacin[8].

Additional drugs omeprazole 20 mg and sucralfat were used because of gastric side effects that were thought to be caused by PAS and ethionamide. Additional drug Alprazolam 0.5 mg is used for side effects of insomnia which are thought to be caused by levofloxacin and moxifloxacin. Risperidone, trihexipenidrile (THP) and merlopam are used for side effects of depression and hallucinations thought to be caused by cycloserine, levofloxacin and etionamide. KSR 600 mg is used for side effects of hypokalemia electrolyte disturbances which are thought to be caused by kanamycin and capriomycin[8].

The use of additional drugs given is in accordance with the Guidelines for Management of Drug-Resistant Tuberculosis (MPTRO) where the drugs are given according to side effects and to a minimum to avoid polypharmacy. Because the more drugs are consumed, the greater the drug interactions that occur. This needs to be paid attention to in elderly patients who have experienced deterioration in organ function that affects the pharmacokinetic processes and pharmacodynamics of drugs in the body[10].

Duration of Treatment

From the results of this study, the highest number of people still undergoing treatment in 2019 was 59 (59%). 18 (18%) of patients who recovered within 9 months, 13 (13%) of patients who recovered within 20 months, 3 (3%) of patients who recovered within 22 months, within 24 months as much as 7 (7%).

9 months MDR-TB treatment was confirmed used a combination of short-term standard OAT / Short Therapy Regimen (STR). The duration of MDR-TB treatment using the STR alloy has two stages, namely the first stage with the second-line OAT injection (Km, Am, Cm) for 4 months every day. If the results of the sputum examination are still positive, the treatment will be added for up to 6 months. Second, the advanced stage, namely treatment is continued for up to 9 months without second-line OAT injection.

Treatment with a duration of 20,22 and 24 months is possible using a conventional standard OAT alloy, individual or XDR regimen with an initial stage of 8-12 months using second-line OAT injection and 12-14 months advanced stages without second-line OAT injection[7]. MDR-TB treatment in patients who recovered was at most 18 (18%) for 9 months because treatment with STR was shorter than conventional standard treatment, individual or XDR regimens during 2017- 2019.

CONCLUSION

The results of these research were treatment of MDR-TB patients mostly uses the standard combination regimen, namely Km-Lfx-Eto-Cs-Z- (H) - (E) as much as 35%, the most common side effect found in the average number was nausea as much as 20.55%, The use of additional vitamin B6 drugs in MDR-TB patients was 92% because treatment using kanamycin, etionamide, levofloxacin and cycloserine had side effects of peripheral neuropathy, From the results of this study, the highest number of people still undergoing treatment in 2019 was 59%.

CONFLICT OF INTERESTS

All author have no to declare

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