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Anti-Tuberculosis Drugs against the Resistance Level of Mycobacterium tuberculosis isolates

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Abstract

Prolonged MDR-TB therapy can have side effects, namely a correlation between cure rates and changes in bacterial profiles related to resistance to anti-tuberculosis drugs (ATD) which can affect the incidence rate of MTB and MDR-TB in a region. The research objective was to analyze the effectiveness of the type of ATD against the resistance level of Mycobacterium tuberculosis (MTB) isolates with the incidence of tuberculosis (TB) and MDR-TB. The research method used was a retrospective cohort based on tracing medical record data at the Surakarta City Center General Hospital 2016 until 2017 with total sampling. The independent variable of this study was the type of ATD, while the dependent variable was the resistance level of MTB isolates. The characteristics of the most patient respondent suspect TB were male with the level of resistance of MTB isolates to ATD relatively varied. The results of the analysis of different tests showed a p value of 0.000 so that the p value was <0.05, so there was an effect of the type of ATD (Strepttomycin, Isoniazid, Rifampicin and Ethambutol) on the resistance of TB isolates from patients with suspected TB. This is useful to determine the success of TB therapy in terms of mortality and the effectiveness of therapy in TB patients.

Introduction

The prevalence rate of TB in Indonesia is 0.4% of all diseases in Indonesia. Based on the results of a survey conducted by the Directorate General of P2P Ministry of Health of the Republic of Indonesia found that in 2017 the province of Central Java was in third place with the number of TB incidents of 42,272 people. The prevalence rate of TB based on clinical diagnosis shows that the incidence of TB in Central Java in 2018 was 0.4%, while according to the Strategic Plan target in 2019 the prevalence of TB was 245 / 100,000 population (Ministry of Health of the Republic of Indonesia, 2018). The incidence rate of tuberculosis (TB) is increasing every year. Meanwhile, the government program on the treatment and control of tuberculosis is continuing to solve this disease, but the increase in the number of cases and deaths is always increasing drastically. Spreading among families often occurs in tuberculosis sufferers and complications also occur due to the incomplete healing process carried out by the sufferer.

TB treatment lasts quite a long time, namely at least 6 months of treatment, causing patients to drop out of treatment or undergo treatment irregularly. Both of these have fatal consequences; which causes treatment to be unsuccessful and the emergence of germs that are resistant to Anti-Tuberculosis Drugs (OAT) or multi-drug resistance (MDR) so that it has an impact on the multiplying of TB treatment costs and complicating TB eradication in Indonesia. The high number of MDR-TB cases

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in Indonesia and TB management that has been carried out through appropriate and safe treatment are expected to reduce the increase in the occurrence of MDR-TB or germ resistance to OAT through increased immunostimulants. In general, MDR-TB occurs because of poor adherence in tuberculosis treatment. MDR-TB is a TB infection caused by Mycobacterium tuberculosis (MTB) and is resistant to isoniazid (H) and rifampin with or without other drug resistance.

The increasing number of TB patients can add to new problems, namely the increase in the number of TB patients and an increase in the incidence of MDR-TB at the Central General Hospital (RSUP) of Surakarta city. RSUP Surakarta was originally known as the Surakarta Center for Community Lung Health in accordance with the Minister of Health Regulation Number 64 of 2015 technically the function is fostered by the Directorate of Referral Health Services as a referral hospital for suspected TB patients located on Prof. Dr. R. Soeharso street Number 28 Surakarta.

Prolonged MDR-TB therapy can have side effects, namely a correlation between cure rates and changes in bacterial profiles related to drug resistance. There is a change in the profile of MTB bacteria related to resistance to OAT, which can affect the incidence rate of MTB and MDR-TB in a region. Therefore, analysis of the effectiveness of OAT used against the resistance level of MTB isolates from TB patients needs to be done to determine the success of TB therapy related to mortality rates and effectiveness of therapy in TB patients. Based on the formulation of the problem and the results of the situation analysis, the aim of the study was to analyze the effectiveness of the type of OAT on the resistance level of MTB patients in RSUP Kota Surakarta.

Methods

The research method was a quantitative descriptive study with a retrospective cohort design based on tracing the medical records of tuberculosis patients at the Center General Hospital of Surakarta City. The independent variable of the study was the type of OAT including Streptomycin, Isoniazid, Rifampicin and Etambutol (SIRE), while the dependent variable was the resistance level of MTB isolates..

Data collection techniques include primary data obtained from tuberculosis patient medical record data at the Center General Hospital of Surakarta City from 2016 to 2017. From the primary data, the editing, coding, scoring and tabulating stages were carried out for further statistical analysis, namely univariate and bivariate analysis. Univariate analysis is an analysis that describes each variable using a frequency distribution table. This univariate analysis of data is presented in the form of a frequency table so that phenomena related to the variables studied will be illustrated. Meanwhile, the bivariate analysis was carried out by using a different test to see if there was a relationship between the independent variable and the dependent variable with the degree of significance $\alpha = 0.05$.

Results and Discussion

Based on primary data from the medical records of suspected TB patients at the Center General Hospital of Surakarta City in 2016 to 2017 as listed in table 1, the characteristics of the respondents including gender and age were obtained based on the identity of the respondents when registering patients who visited the at Center General Hospital of Surakarta City.

Table 1. Distribution of Respondent Characteristics

No.	Description	In 2016		In 2017	
		Number	%	Number	%
1	Gender				
	Male	249	66,22	120	60,91
	Female	127	33,78	77	39,09
2	Ages				
	< 18 Years Old	7	1,86	2	1,02
	18-25 Years Old	52	13,83	28	14,21
	26-35 Years Old	71	18,88	42	21,32
	36-45 Years Old	63	16,76	36	18,27
	46-55 Years Old	73	19,41	36	18,27
	56-65 Years Old	65	17,29	34	17,26
	> 65 Years Old	45	11,97	19	9,64
	Total	376	100	197	100,0

Based on table 1, the characteristics of respondents according to gender indicate that the majority of respondents suspect TB is male, namely in 2016 amounted to 66.22% and in 2017 amounted to 60.91%. TB infection is generally related to the level of infection occurring in the lung organs and is influenced by the behavior of respondents, namely smokers, and the majority of smokers are male than female. In addition, in general, men are the backbone or family responsibility, which is strongly influenced by socio-economic, cultural and environmental conditions, including factors of type and work load, total income, education level, lifestyle or habits and the environment in which they live. The results showed that the prevalence of TB in male was higher than in female as happened in China where the ratio of male and female reached 2.01 (1,303 / 647) with the percentage of male patients 67.49% and 32 female. , 51%. The level of drug resistance in male to TB was significantly higher than in female. This may be due to differences in population distribution and different study periods (Q. Li et al., 2018).

Apart from gender, age also affects the incidence of TB infection. As table 1 shows the characteristics of the respondent suspect TB occurred relatively in the productive age to adulthood, namely 26-55 years old. Age is an independent factor related to MDR-TB and significantly occurs in the age 45–65 years old. Productive age to adulthood is the age of optimum activity carried out by respondents in relation to socio-economic conditions. The distribution of TB patients shows that a percentage of more than 50% occurs in productive age, namely 20 and 50 years old, this is related to social relations and working conditions of respondents (Liu et al., 2018). The results of previous studies indicated that respondents aged over 60 years old had a significantly lower percentage of the incidence of MDR-TB and / or XDR-TB than those in the younger age group. This is thought to be related to the workload, study and life loads that are greater while the lifestyle of the elderly is relatively simpler. The level of resistance to OAT in respondents aged over 60 years in reinfection cases was significantly lower than for other age groups due to an imbalance of drug resistance between different age groups mainly due to history of treatment (Ullah et al., 2016).

Other factors that influence the occurrence of TB disease include socioeconomic conditions, age, gender, nutritional status and smoking habits. In general, the education level of the suspect TB patients was relatively low and correlated with their socioeconomic life. The low level of education of TB patients, will have difficulty or lack of understanding of guidelines for the treatment of drug-resistant tuberculosis and its effects. In terms of socio-economic conditions, namely due to the low level of welfare due to unemployment or retirement and insufficient nutritional needs that affect stressor factors and smoking behavior. The number of new TB cases in Indonesia was 420,994 cases in 2017. The percentage of smokers occurred in males as much as 68.5%, while females were only 3.7%. In addition, the number of new TB cases in males was 1.4 times greater than that in females. This happens because men are more easily exposed to the risk of TB due to smoking and less adherence to taking medication. Although smoking is not the main cause of tuberculosis, smoking can reduce the immunity of smokers because the toxins in cigarettes are harmful to health, namely tar, nicotine, CO gas, and NO that come from tobacco so that people are more susceptible to TB bacterial infection. Smoking habits make a person more susceptible to TB infection, and the death rate from TB will be higher in smokers compared to nonsmokers. Smoking habits can also damage the lung defense mechanism called muccociliary clearance. In addition, cigarette smoke can increase airway resistance and cause easy leakage of blood vessels in the lungs, it will also damage macrophages, which are cells that can eat harmful bacteria. Individuals who are exposed to secondhand smoke or secondhand smoke have a higher potential for exposure to TB than active smokers. TB in smokers is more contagious than non-smoking TB sufferers, smoking habit is also a factor in the progression of pulmonary tuberculosis and the occurrence of fibrosis (Sarwani, Nurlaela, & Zahrotul, 2012).

Since 2010, WHO has recommended the Molecular Rapid Test (TCM) as the initial examination for the diagnosis of MDR-TB. The TCM method is a new revolution in TB diagnosis

that contributes to the rapid diagnosis of TB and MDR-TB cases within 2 hours compared to conventional culture and sensitivity testing methods which take 3-4 months. The results of the MDR-TB diagnosis of the TCM method can be used as a basis for patient treatment but does not exclude the need for culture and sensitivity testing for OAT because TCM only detects first-line OAT-resistant TB, especially against rifampicin. Immunity to INH must be confirmed by a culture examination followed by an OAT sensitivity test (Sun et al., 2019). Diagnosis of TB-RO, MDR-TB and XDR-TB can be done using a rapid test of the PCR method (Xpert MTB / RIF), culture examination and a germ sensitivity test for OAT, namely the Drugs Sensitivity Test (DST). A rapid and sensitive diagnostic test method needs to be done to support adequate MTB examination results and MTB therapy strategies (Weldegebreal & Mebrahtu, 2017).

Table 2. Distribution of MTB Sensitivity and Resistance Test Results Against OAT

No.	DST results	In 2016		In 2017	
		Number	%	Number	%
	Resistant	170	45,21	47	23,86
	Sensitive	206	54,79	150	76,14
	Total	376	100	197	100,0

Source: Primary Data, 2017

Based on table 2, it shows the distribution of sensitivity test results for MTB isolates to OAT in RSUP Kota Surakarta, showing the percentage of resistance and sensitivity that varies, namely the percentage of sensitivity of 54.79% and resistance of 45.21% in 2016; whereas in 2017 the percentage of sensitivity was 76.14% and resistance was 23.86%. The DST stage is carried out after a positive smear microscopic examination result or a positive TCM examination result. DST uses Lowenstein Jensen (LJ) solid media containing OAT, namely Streptomycin, Isoniazid, Rifampicin and Etambutol (SIRE). The varying levels of resistance or sensitivity of MTB isolates to OAT are influenced by several factors including different characteristics of respondents related to the level of TB infection of respondents suspect initial TB or the MDR-TB group. DST laboratory examination results can be influenced by HR factors (Human Resources) related to soft skills and hard skills of TLM (Medical Laboratory Personnel) in conducting examinations, strengthening internal quality including laboratory facilities and infrastructure, standardization of tests in order to ensure the reliability and validity of examination results, limits expired diagnostic reagent, type of examination method, recording and external laboratory testing includes recording and reporting of examination results or medical record data. However, DST is a direct method of susceptibility testing for M. tuberculosis as one of the laboratory diagnostic parameters used in determining the level of germ resistance. Another factor that affects the in vitro DST results is the sensitivity and specificity of each examination method (Harti, Murharyati, Sulisetyawati, & Oktariani, 2018). The ideal examination method is to meet the specificity, sensitivity and representative criteria so that each method has weaknesses and strengths. The results of the sample culture carried out are part of the sensitivity test for M. tuberculosis to drugs and to determine the potential for MDR-TB (Lu et al., 2017).

MDR-TB is a type of TB bacillus resistance to at least two first-line OAT, namely isoniazid and rifampin; which are known to be the two most effective types of OAT. Germicidal resistance to OAT can occur if the administration of drugs is not appropriate, namely the patient does not complete the treatment given, the health worker provides inappropriate treatment, whether in combination, dosage, length of treatment and quality of the drug, as well as the problem of drug supply which is not always available. MDR-TB is a major public health problem due to the presence of a strain of M. tuberculosis that is resistant to first-line OAT, including rifampin and isoniazid simultaneously. A patient who is confirmed to have MDR-TB can pass this form of TB to other people. MDR-TB

sufferers usually occur in individuals who have a history of previous TB treatment compared to new cases of patients. A history of TB treatment increases the risk of MDR-TB incidence, this is related to previous treatment results, namely dropping out of treatment, failing treatment, relapse, or patients who have had MDR-TB treatment (Kobayashi, Hattori, Akter, Mizoue, & Ohta, 2017). The need for monitoring OAT therapy through routine culture examinations for TB patients during the treatment process (Mitnick et al., 2016)

Table 3. TB Category Distribution

No.	TB Category	In 2016		In 2017	
		Number	%	Number	%
	MTB	206	54,79	47	23,86
	MDR-TB	170	45,21	150	76,14
	Total	376	100	197	100,0

Source: Primary Data, 2017

Based on table 3, it shows that the percentage distribution of the incidence rate of MDR-TB and MTB in 2016 and 2017 at the Surakarta City Hospital is relatively varied. In 2016 the percentage of MDR-TB occurrence (45.21%) was lower than that of MTB (54.79%) while in 2017 the incidence rate of MDR-TB (76.14%) was higher than that of MTB (23.86%). The decrease or increase in the percentage cannot be used as a guide or reference that MDR-TB cases are lower than MTB due to various factors that influence the rate of MDR-TB occurrence in a region. Many factors contribute to drug resistance and the occurrence of MDR-TB, including in Indonesia. This is due to the patient's ignorance of the disease, poor patient adherence, ineffective administration of monotherapy or drug regimens, inadequate doses, poor instructions, low medication regularity, lack of motivation, irregular drug supply, poor bioavailability and quality. drugs contribute to secondary drug resistance. The percentage distribution of resistance levels and / or sensitivity of MTB isolates to the type of OAT SIRE in Center General Hospital of Surakarta City is as listed in the table 4.

Table 4. Resistance Level of MTB Isolates To SIRE

No	Types of OAT	In 2016						In 2017					
		Resis-tent	%	Sensitive	%	Mean Rank	P value	Resis-tent	%	Sensitive	%	Mean Rank	P value
1	S (Strepto-mycin)	154	40,96	222	59,04	541,50	0,000	39	19,80	158	80,20	346,00	0,000
2	I (Iso-niazid)	21	5,59	355	94,41	807,50		11	5,58	186	94,42	402,00	
3	R (Rifam-pycin)	12	3,19	364	96,81	825,50		5	2,54	192	97,46	414,00	
4	E (Etham-butol)	7	1,86	369	98,14	835,50		3	1,52	194	98,48	416,00	

Source: Primary Data, 2017

Based on table 4, it shows that MTB isolates from suspected TB patients in the Surakarta City Hospital showed the highest percentage of sensitivity to Ethambutol, amounting to 98.14% in 2016 and 98.48% in 2017. Based on this, Ethambutol is the most effective type of OAT for therapy. MTB and / or MDR-TB rather than Streptomycin, Isoniazid or Rifampicin. The results of the different test analysis showed a p value of 0.000 so that the p value <0.05, then there was an effect of the type of OAT SIRE on the resistance and sensitivity of TB isolates from patients with suspected TB. The resistance factor of MTB isolates to the type of OAT had an impact on the incidence rate of MDR-TB.

The effectiveness of a type of OAT on the level of resistance or sensitivity of M. tuberculosis isolates is very much influenced by the mechanism of action of the drug, namely

related to the chemical physical properties of medicinal compounds to penetrate the cell walls of TB bacteria; and the optimum dose required to be bactericidal. In addition, it is also influenced by environmental factors such as acidity, temperature, enzymatic activity and physiological factors of M. tuberculosis cells related to the structure and composition of the cell wall and biomolecular genetic expression. (Y. Li et al., 2016). The level of resistance of MTB to OAT can occur through two main mechanisms, namely primary resistance of MTB to OAT during transmission to a new host and secondary resistance due to mutations in genes that are resistant to one or more OATs. (Sowajassatakul, Prammananan, Chaiprasert, & Phunpruch, 2014). The mechanism of action of OAT including isoniazid (INH) is thought to work by inhibiting the synthesis of mycolic acid, the main component of MTB cell wall. Rifampicin (RIF) is bactericidal through inhibition of nucleic acid synthesis, namely transcription RNA synthesis by binding to the β subunit of RNA polymerase. Pyrazinamide (PZA) is a structural analogue of nicotinamide, bactericidal against semidorman tubercle bacilli in acidic conditions. Under acidic conditions, tubercle bacilli produce pyrazinamidase, an enzyme that converts PZA to pyrazinoic acid, which acts as an antibacterial. Ethambutol (EB) can interfere with carbohydrate metabolism, while streptomycin (SM) kills bacteria by interfering with protein synthesis, translation, by binding to 16s rRNA. INH is the most effective OAT both for treatment and prevention of TB disease because M. tuberculosis is very sensitive to INH. INH resistant lines often appear with a frequency of approximately 90%. Resistance to INH is caused by mutations in one of the katG, inhA or ahpC genes. Previously, TB could be cured with the proper administration of anti-tuberculosis, however, recently many M. tuberculosis strains were found to be resistant to two or more OATs known as MDR-TB strains. Initial treatment of pulmonary TB caused by M. tuberculosis usually uses isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EB) or streptomycin (SM) as the main options. Resistance encourages the use of other more toxic alternative drugs, namely ethionamide, aminosalicylic acid, cycloserine, capreomycin, ciprofloxacin or ofloxacin. The emergence of M. tuberculosis strains that are resistant to two or more anti-tuberculosis drugs (OAT) causes the failure rate of tuberculosis therapy to be high. The high level of resistance of MTB to rifampin suggests a potential increase in the incidence of MDR. Therefore, a TB control program is needed by the related government agencies or institutions (Adane, Ameni, Bekele, Abebe, & Aseffa, 2015).

The incidence of MDR-TB is an important public health problem and is a global disease (McBryde et al., 2017). The emergence of multidrug-resistant tuberculosis (MDR-TB) and multiple drug-resistant tuberculosis (XDR-TB) around the world has posed additional challenges to global tuberculosis (TB) control efforts, because of the limited treatment options available and treatment outcomes are often sub- optimal (Alene et al., 2017). Data from WHO in 2018 shows that the number of TB cases that are resistant to rifampin (RR-TB) is estimated to reach 201.8 million worldwide in 2017, and 82% of these cases are MTB that is resistant to several types of drugs, namely the least isoniazid and rifampin. In 2017, it was estimated that among MDR-TB cases there were 8.5% of TB cases that were widely resistant to drugs, namely MTB-XDR, resistance to isoniazid, rifampin, one fluoroquinolone, and one second-line drug. The duration of MDR-TB treatment is relatively longer than non-MDR-TB longer than drug-sensitive TB and expensive treatment costs. Recent data on the results of therapy show that the treatment success rate for TB treatment is up to 82%; 55% for MDR / RR-TB and 34% for XDR-TB. The proportion of MDR or XDR-TB incidence rates in China was higher in recurrent treatment cases than in initial TB cases and the level of MTB resistance to OAT was influenced by factors of age, sex and region or region and standardized TB therapy could reduce the incidence of MTB resistance to OAT and reinfection of TB (Wu et al., 2019).

Determination of the incidence of MDR-TB and MTB as a useful determinant for early and accurate detection of mortality rates and effectiveness of therapy in TB patients. The distribution of the level of occurrence of MTB and MDR-TB in suspected TB patients is

influenced by various factors that contribute to the occurrence of germicidal resistance to drugs, respondent characteristics, treatment programs, culture, socio-economic and environmental conditions. Variables that influence the incidence of MDR-TB include family support, knowledge, regularity of taking medication and the activeness of staff. In addition, tuberculosis patients who do not regularly drink OAT are at risk of experiencing MDR-TB. The knowledge of pulmonary TB patients about TB disease, the required treatment and the length of treatment that must be done will affect the patient's adherence to complete treatment. Patients with low knowledge level will have more than twice the risk of treatment failure compared to patients who have high knowledge. Respondents with poor medication adherence had a 2.486 times risk of developing MDR-TB disease compared to respondents who were adherent in taking OAT on TB treatment. Education, knowledge, behavior, social support, and self-efficacy are related to adherence to treatment of TB patients. Low levels of education, lack of family support, and medical services related to tuberculosis are associated with low adherence to medication.

Pulmonary TB treatment generally consists of an intensive phase for 2-3 months and a follow-up phase for 4 months. TB drugs should be taken regularly for 6-8 months according to schedule. Treatment regularity less than 90% will affect healing. OAT must be taken regularly according to schedule, especially in the two phases of treatment to avoid treatment failure and relapse. TB treatment in the intensive phase needs to be considered and carried out according to the procedure and schedule because of the inaccuracy of the implementation of the intensive phase of treatment, that is, if the TB patient does not regularly take medication, it will have an impact on conversion failure at the end of the intensive phase of treatment and the emergence of MDR-TB problems. The results showed that the success of MDR-TB treatment using a long-term regimen in MDR-TB patients in 2013-2015 was only 49.7%. The previous TB-RO treatment regimen took so long that in May 2016, WHO recommended a new TB-RO treatment, using short-term guidelines. This new regimen aims to streamline the patient's treatment period so that it is not too long so that it can reduce patients who drop out of treatment. With a long treatment time, TB-RO patients are at risk of dropping out of treatment and leading to treatment failure. Shorter treatment duration with the effectiveness of faster treatment results, is expected to increase treatment enrollment, reduce the number of patients dropping out of treatment and increase the success rate of treatment in TB-RO patients so that standard short-term treatment guidelines for drug resistance patients began to be implemented in Indonesia in 2017.

The treatment success rate of TB-RO patients is still low because the management of drug-resistant treatment is much more difficult and requires a long duration of treatment, namely a minimum of 20 months. Another problem related to TB-RO management that is currently available around the world is costly both for the program and for the patient. Therefore, TB control in health services primarily requires effective strategic steps. Practical measures include support for program activities, high-quality training for medical staff and raising public awareness about TB prevention and control including routine DST activities for TB patients from high burden areas and limited resources to reduce the global burden of TB. (Lan, Li, Chen, Zhang, & Zhang, 2019).

The strategies used in controlling tuberculosis include prevention of transmission, case finding, treatment and intensive treatment of TB-RO patients until they recover with passive case treatment as a standard operational procedure for TB control in Indonesia, which requires patients to go to Puskesmas. Sufferers are hindered by location, transportation, economic conditions. Management of therapeutic services in addressing TB-RO treatment non-adherence is the key to achieving program success. According to WHO, TB-RO control is influenced by the role of health workers, efforts to provide therapy services in health facilities and patient behavior. Treatment less than 12 months can result in a risk of treatment failure, and a greater risk of transmission, cause medical and psychosocial problems, and become a global community problem, as it contributes

to increased morbidity and mortality. MDR-TB therapy uses several types of drugs, causing several problems in terms of tolerance to these drugs. The response of each individual is unpredictable, but treatment should not be stopped just because of fear of the reaction.

The MDR-TB control program is a new challenge for the Indonesian government because of difficult diagnosis, high rates of therapy failure and mortality. Treatment for MDR-TB sufferers is relatively more difficult, with a success rate of only about 50% and expensive treatment costs, even up to 100 times more expensive than TB treatment without MDR, so that developing countries including Indonesia becomes a very heavy burden in efforts to overcome it. Treatment of TB-RO, MDR-TB, and XDR-TB is more difficult when compared to the treatment of sensitive TB germs. The success rate of TB treatment can be done quickly if TB cases have been identified early and the effectiveness of the treatment program. TB and MDR-TB treatment is relatively long, namely 18-24 months, but the TB treatment program must be integrated because if a failure occurs it will have an impact on various things, including the high cost of treatment. The price of second-line TB drugs is much more expensive, which is 100 times more than ordinary TB treatment and its handling is relatively more difficult. (Flora et al., 2013). Apart from the complicated treatment mix, the number of drugs is more and the side effects caused are also heavier. Several factors that must be considered that greatly affect the success of treatment, such as the length of time for treatment, compliance and regularity of patients for treatment, immune system, as well as the socio-economic factors of patients who are no less important. Treatment that is interrupted or not in accordance with DOTS standards can also result in the emergence of multiple cases of immunity to Anti-Tuberculosis Drug which results in a stronger type of TB germ, namely the occurrence of MDR-TB. MDR-TB treatment requires more expensive and longer time with the success of treatment is uncertain. The most dominant variable influencing the incidence of MDR-TB was medication adherence; Therefore, it is necessary to increase the extension program to patients and families about the importance of medication adherence and the consequences that arise from non-adherence to taking medication so that this can be used to control the increase in the incidence of MDR-TB.

Medical personnel, especially doctors and nurses, need to provide therapeutic services to patients, especially in an effort to improve drug-resistant tuberculosis patient adherence to treatment, in order to avoid the spread of drug-resistant tuberculosis more widely and prevent XDR-TB. In addition to health services, family and community support is needed, namely the need for a strong commitment to healing in patients, Active Case Treatment from officers, family psychosocial support and family support systems to become caregivers to prevent extensively drug resistance. Family support for having compliance to Anti Tuberculosis Drug shows the effect of family support on adherence to taking anti-tuberculosis drugs, the higher the family support the higher the level of compliance of patients with taking Anti Tuberculosis Drug. The role of the family in the care of TB sufferers includes: looking after and caring for the sufferer, maintaining and improving mental status, anticipating socio-economic changes, providing motivation or support and facilitating the patient's spiritual needs. High family support will reduce the morbidity and mortality rates of sufferers. The quality of life of TB patients who undergo treatment depends on their physical condition, emotional distress, individual and family coping, social support from family and people around them, and the environment that supports pulmonary TB patients in their life. Good adaptation methods in undergoing boredom and obstacles during long treatment for MDR-TB patients are based on the process of self-awareness in the form of creating motivation to change, strong support systems, continuous and continuous coaching efforts. A concerted effort from stakeholders, supporters and research is needed for the development of a shorter, more effective and safer regimen of Anti Tuberculosis Drug (Tiberi et al., 2018).

Complete TB control can be pursued by implementing a 3 pillar strategy, namely integrated patient-focused treatment and prevention; integrated policy and support

systems and intensive and innovative TB research in the search for TB drugs (Migliori et al., 2020). The key to preventing MDR-TB is early diagnosis of any suspected drug resistant TB and followed by treatment with standard of Anti Tuberculosis Drug. The application of standardized TB treatment using standardized of Anti Tuberculosis Drug is very important for controlling TB and the incidence rate of MDR-TB effectively, especially in monitoring adherence and completeness of treatment, and must be reported into the surveillance system.

Conclusion

The results of the analysis of the difference test showed a p value of 0.000, so that the p value <0.05, then there was an influence on the type of Anti Tuberculosis Drug (OAT) (Strepttomycin, Isoniazid, Rifamicin and Ethambutol) against resistance to TB isolates from patients with suspected TB.

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