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Research Article

Evaluation of therapeutic effectiveness of antituberculosis injection based on conversion time in drug-resistant tuberculosis

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Abstract

Drug-resistant tuberculosis is a condition in which *Mycobacterium tuberculosis* is resistant to first-line anti-tuberculosis drugs, namely isoniazid and rifampicin, which are the two most effective anti-tuberculosis agents. Conversion time is a parameter to assess whether the therapeutic effect of injection has been achieved by carrying out two acid-resistant bacilli (ARB) sputum examinations within a maximum period of 2 consecutive months. Kanamycin and capreomycin are injectable drugs that are used in the intensive phase. This cross-sectional study aimed to evaluate the therapeutic effect of injection using ARB sputum conversion time and to analyze other factors related to ARB sputum conversion time. The study used retrospective data from patients' medical records, collected with purposive sampling technique. The results of the study showed that from 101 patients who met the inclusion criteria 57.4% used kanamycin and 42.6% received capreomycin. The therapeutic effect was achieved in 87.1%. There was no significant correlation between the type of injection therapy and therapeutic effectiveness (p-value = 0.983). In conclusion, therapy using injections for drug-resistant tuberculosis is effective but still requires close monitoring due to the high adverse drug reaction (ADR).

Keywords

antituberculosis injection, therapeutic effectiveness, drug-resistant tuberculosis

Introduction

Drug-resistant tuberculosis is a global public health problem. The Global Tuberculosis Report in 2019 reported that there were 186,772 cases of multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis detected, and in 2018 there were 156,071 registered cases of under treatment, while in 2017 there were 139,114 cases of multidrug-resistant tuberculosis (WHO 2021). The incidence of drug-resistant tuberculosis at Dr. M. Goenawan Partowidigdo Lung Hospital, Bogor regency, Indonesia has escalated from 0.043% in 2015 to 0.370% in 2016. Drug-resistant tuberculosis treatment uses at least four anti-tuberculosis drugs that are still sensitive to *Mycobacterium tuberculosis* bacteria, including those delivered as injections. The drugs that are delivered in injection dosage form are kanamycin and capreomycin, which belong to the aminoglycoside group (WHO 2023). These two drugs work by inhibiting protein synthesis (Sri et al. 2010). Kanamycin is widely used and is included in the standard regimen in Indonesia (Septyani et al. 2020). Kanamycin is very polar so it is difficult to be absorbed in the digestive tract. Kanamycin should be given parenterally via intramuscular injection and used for at least 4–6 months after ARB sputum conversion occurs (Sri

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et al. 2010). Capreomycin is an alternative option, used by patients who are kanamycin-resistant (Arnold et al. 2017).

Drug-resistant tuberculosis treatment consists of two phases, an intensive phase (short-term therapy) and an advanced phase (long-term therapy). The intensive phase uses injectable drugs (kanamycin or capreomycin) which are used for at least six months or four months after BTA sputum conversion. An advanced phase is used after the injection is stopped, which lasts for a minimum of 18 months after conversion of ARB sputum. ARB sputum conversion time is a parameter to see whether the therapeutic effect of injection has been achieved. There needs to be an assessment before deciding whether the patient is in the short-term or long-term category. Long-term is often used for individual regimen (Carolia and Mardhiyyah 2016; Alipanah et al. 2018).

The prevention program has made various breakthroughs to increase the coverage and quality of drug-resistant tuberculosis services in Indonesia. One of which is the implementation of treatment without injection, both short and long-term. In 2019, WHO issued recommendations regarding the use of drug-resistant tuberculosis treatment without injection, where the injection drug kanamycin or capreomycin is replaced with the drug bedaquiline (Sharma and Dheda 2019). There is still minimal research regarding the effects of kanamycin or capreomycin on ARB sputum conversion time, especially in the Indonesian population. The cure rate for TB is still low and there are changes in treatment guidelines that have attracted attention to evaluate the previous treatment process which used injection therapy. The cure rate for TB is still low and there are changes in treatment guidelines. It is necessary to evaluate the therapeutic effects of injection in the Indonesian population. This study aimed at investigating the ARB sputum conversion time in patients using kanamycin or capreomycin injections, specifically on the ADR of both injections. This study further assessed the correlation of ADR and ARB sputum conversion time.

Study design

This is a cross-sectional study using retrospective data of medical records from drug-resistant tuberculosis patients at Dr. M. Goenawan Partowidigdo Lung Hospital. This study was approved by the Ethic Committee of Immanuel Hospital Bandung (004/KEPK/IKI/2023).

Study sample

Purposive sampling was used in this study, using outpatients that received the treatment during the period of 2017–2022. The inclusion criteria were outpatients with drug-resistant tuberculosis who were ≥17 years old and had complete medical records including patient identity, treatment regimen, duration of treatment, dose and amount of medication, treatment history, laboratory tests, sputum ARB conversion time, and end results of treatment. Exclusion criteria consisted of drug-resistant tuberculosis with diabetes mellitus, HIV-AIDS, other respiratory disorders such as pneumonia, bronchitis, lung cancer, psychiatric disorders, liver and kidney function disorders, and pregnant-breastfeeding women.

Therapeutic effectiveness

The therapeutic effectiveness was based on the sputum ARB conversion to negative, obtained from ARB examination carried out twice within a maximum period of two consecutive months. Success was achieved when two ARB examinations in two consecutive months are negative.

Data analysis

Univariate analysis was used for the data on the frequency distribution of age, gender, length of therapy, number of drugs used, and laboratory examinations. While the bivariate was utilized to analyze the correlation between type of injection used and the achievement of therapeutic success and the multivariate analysis was used to assess the correlation of other factors with this achievement.

Result

Patient characteristic

A total of 234 patients were tested of which 101 met the inclusion criteria. The patients were categorized based on age, gender, amount of oral medication used, and duration of treatment (Table 1).

Table 1. Drug-resistant tuberculosis patient characteristic.

Characteristic	No of patients	Percentage (%)
Age (years)		
17–25	27	26.7
26–35	37	36.6
36–45	20	19.8
46–55	10	9.9
56–65	7	6.9
>65	0	0
Gender		
Female	44	43.6%
Male	57	56.4%
Amount of oral medications used		
1–5 of medications	7	6.9%
> 5 of medications	94	93.1%
Medications used		
Delamanid	1	16.5
Bedaquiline	3	16.0
Linezolid	3	10.2
Isoniazid	35	16.5
Clofazimine	36	10.7
Moxifloxacin	37	10.9
Levofloxacin	61	5.8
Cycloserine	64	0.2
Etambutol	96	4.0
Pirazinamide	99	0.5
Ethionamide	99	0.5
Duration of treatment		
Long (18–24 months)	61	60.4
Short (9–11 months)	40	39.6

A total of 83.1% of patients were aged 17–45 years and 16.8% were over 46 years old. There were no patients classified as elderly. The majority of them were male (56.4%). The majority of patients (93.1%) received >5 of medication. Besides injection, patients also received oral therapy. The most commonly used drugs were pyrazinamide (16.5%), ethionamide (16.5%), ethambutol (16.0%), cycloserine (10.6%), and levofloxacin. (10.1%). Levofloxacin was used for long duration of treatment (18–24 months). These drugs are by the treatment regimen listed in the drug-resistant tuberculosis guidelines in Indonesia. The most widely used treatments were long-term regimens (60.4%). The factor that caused treatment to take longer was the length of time for ARB conversion, where ARB examination in 2 consecutive months did not show negative results. The selection of long-term therapy was also adjusted to the clinical condition of the patient. For example, there were patients with a history of relapse drug-resistant tuberculosis. The past treatments include ethambutol, levofloxacin, cycloserine, and kanamycin injection. The patients were also confirmed to be rifampicin-resistant, indicated by the results of a drug sensitivity test. The administration of vitamin B6 was also used in patients taking INH or cycloserine. The aim is to overcome the neurotoxic effects from INH or cycloserine. The use of cycloserine is also shown in the neurotoxic effects (peripheral neuropathy) like INH. So, some literature recommended using vitamin B6 to overcome it (Mukherjee et al. 2017; Court et al. 2021; Part 2022).

Overview of the type of injection

The most widely used injection is kanamycin at 57.4%, and capreomycin at 42.6% (Table 2). Kanamycin is the first choice of injectable drug regimen in Indonesia. Capreomycin is used for patients allergic to kanamycin (Septyani et al. 2020). These results are in line with earlier data reported by (Zulkarnain et al. 2023) where the use of kanamycin was higher, namely 61.61%. The use of kanamycin or amikacin as the first choice has been based on the high rate of streptomycin resistant, the lower cost, and lower ototoxic side effects (Chakroborty 2011).

Table 2. Overview of the type of injection.

Type of injection	No of patients	Percentage
Kanamycin	58	57.4
Capreomycin	43	42.6
Total	**101**	**100**

The therapeutic effectiveness and its correlation with the type of injection

Based on the assessment of ARB conversion, as presented in Table 3, it was found that the therapeutic effectiveness was 87.1%.

There were patients of productive age who showed sputum ARB conversion only in the 9th month of treatment. As shown in Table 4, the Chi-square test showed no correlation between the type of injection and achievement of therapeutic effectiveness.

Table 3. Achievement of therapeutic effectiveness.

Therapeutic effectiveness	No of patients	Percentage
Achieved	88	87.1
Not achieved	13	12.9
Total	**101**	**100**

Table 4. Correlation between the type of injection and with achievement of therapeutic effectiveness.

Type of injection	Achieved	Not achieved	No of patients	*p*-value (95%CI)
Kanamycin	50	8	58	0.983*
Capreomycin	38	5	43	
Total			**101**	

Evaluation of final results of treatment

An assessment of final results of treatment found that 93 (92.1%) patients experienced a cure, 7 (6.9%) had complete treatment, and only 1 (1%) patient failed. Patients were classified as cured when they completed the treatment without evidence of failure and tested negative for sputum examination (at least 3 times consecutively with a minimum of a 30 day-interval between examination during the follow-up stage) (Indonesia Ministry of Health 2020). Meanwhile, patients with complete treatment were those who had undergone treatment for more than 18 months and tested negative for ARB sputum examination. Patients were categorized as having failed if they dropped out of treatment or did not complete the treatment course. The final results of treatment are presented in Table 5.

Table 5. Final results of treatment.

Final results	No of Patients	Percentage
Cure	93	92.1
Complete	7	6.9
Failure	1	1
Total	**101**	**100**

Apart from evaluating the conversion time and final treatment results, supplementary lab examinations were also carried out. This lab examination is obtained from the results of lab examinations for each patient in each month of the control patient which are recorded in the patient's medical record. This lab examination profile is supporting data for the possibility of ADR. The data shows that the majority of patients experienced impaired hematocrit and increased uric acid (Table 6). These results are in line with earlier data showing uncontrolled hematocrit levels in drug-resistant tuberculosis (Hutauruk 2021).

Correlation of other factors with the achievement of therapeutic effectiveness

The present results showed that age did not have a significant effect on therapeutic effectiveness, which contradicted other studies (Khan et al. 2019). Gender, length of therapy, and number of oral medications also had no

Table 6. Result of laboratory examinations.

Parameter	Normal		Abnormal	
	N	%	N	%
Hemoglobin	47	38%	47	3.8%
Leukosit	58	4.6%	36	2.9%
Hematocrit	44	3.5%	51	4.1%
Eritrosit	58	4.6%	37	3.0%
Trombosit	61	4.9%	34	2.7%
SGOT	84	6.7%	8	0.6%
SGPT	84	6.7%	8	0.6%
Ureum	52	4.2%	47	3.8%
Creatinin	92	7.4%	7	0.6%
Uric acid	41	3.3%	58	4.6%
Sodium	96	7.7%	3	0.2%
Clorida	92	7.4%	7	0.6%
Calium	77	6.2%	22	1.8%

significant correlation with effectiveness (respective p-value: 0.391, 0.44, and 0.368), which are also not in line with earlier results (Tirtana 2011).

Discussion

The present study showed that the majority of patients belonged to productive age and male categories. This is in line with an earlier result by (Wibowo et al. 2021) where the majority of patients suffering from drug-resistant tuberculosis were those aged 18–40 years. The present results were further supported by a report from other research showing that drug-resistant tuberculosis sufferers were mostly patients in the age range of 26–45 years old (Albaihaqi et al. 2021). Productive age is one of the risk factors for drug-resistant tuberculosis because, at this age level, the rate of transmission of tuberculosis bacteria is very high, and high work activities result in sufferers tending to be non-compliant in taking medication during previous tuberculosis treatment, causing drug resistance to develop (Bawonte et al. 2021). Apart from productive age, the majority of patients were male, a data which is in line with that reported by the previous study (Aviana et al. 2021). The smoking habit makes a person more easily infected with tuberculosis. Patients who have been infected with tuberculosis but still smoke can develop drug-resistant tuberculosis due to the damage to the lung defense mechanism, the mucociliary clearance (Nugroho et al. 2018).

A multiple medications strategy, consisting of ≥5 drugs, is used for drug-resistant tuberculosis. The treatment strategy for patients in the present study followed a guideline for drug-resistant tuberculosis, comprising oral medications and injection. Currently, oral drugs commonly used are levofloxacin, cycloserine, pyrazinamide, ethionamide, and ethambutol for the initial phase, and the same regimen without pyrazinamide in the advanced phase (Aminah S. et al. 2014).

Pyrazinamide is a drug used in the treatment of drug-resistant tuberculosis which is only active against tuberculosis bacteria in acidic conditions (pH 5.5) (Nath and Ryoo 2013). Most drug-resistant tuberculosis sufferers have chronic inflammation in their lungs, where theoretically the lungs produce an acidic environment, and pyrazinamide can work actively in an acidic environment (WHO 2021). Likewise, the use of ethambutol is useful for stopping the growth of bacteria that cause tuberculosis. Ethionamide also supports treatment where ethionamide is bacteriostatic, working by suppressing the growth of tuberculosis bacilli that are resistant to isoniazid and streptomycin. Some of the side effects that can occur after consuming ethambutol include nausea or vomiting, stomach ache, joint pain, headache or dizziness, indigestion and loss of appetite, visual disturbances with visual impairment, and color blindness. If initial problems with vision occur, ethambutol must be stopped immediately. This ocular side effect is reversible (Dave et al. 2021; Rana et al. 2022; Shah et al. 2022).

Ethionamide is a second-line anti-tuberculosis drug used to treat drug-resistant tuberculosis which is resistant to isoniazid and streptomycin. The mechanism of action is the same as isoniazid which inhibits protein production, prevents mycolic acid biosynthesis, and affects bacterial cell membranes (Wang et al. 2007). *In vivo*, these two pyridine derivatives can kill bacteria. Ethionamide shows the highest kill rate and plays a major role in drug-resistant tuberculosis regimen, in combination with levofloxacin. Ethionamide has a profile of correlation between minimum inhibitory concentration (MIC) and time-to-sputum conversion. The pharmacokinetics of ethionamide showed that it is not metabolized in the liver and is excreted unchanged in the urine (Mugabo and Mulubwa 2021).

Levofloxacin is the fluoroquinolone group that was most widely used in this study compared to moxifloxacin. Levofloxacin, apart from its activity against gram-positive and negative bacteria, has been shown to have quite good activity against tuberculosis bacteria (York et al. 2008; Ghimire et al. 2019). Levofloxacin also shows good outcomes when used in patients with drug-resistant tuberculosis (Andrade and Tulkens 2011; Ghimire et al. 2019; Nibell et al. 2022; Rusu et al. 2023). However, the use of levofloxacin can also cause several ADR such as liver disease and hyperuricemia (Carroll et al. 2012; Koh et al. 2013; Ghimire et al. 2019; Rusu et al. 2023).

Drug-resistant tuberculosis has traditionally been treated with the aminoglycoside antibiotic kanamycin. Intravenous kanamycin is a second-line medication. There is no discernible difference in the effectiveness of intravenous kanamycin versus oral therapy. Patients who take kanamycin have a recovery rate that is nearly identical to that of patients who do not receive an injection (>50%). It is evident that kanamycin is still categorized as a medicine for injection with good efficacy. ADRs, such as nephrotoxicity and hearing loss, have also been described in addition to the good efficacy of kanamycin (Cegielski et al. 2021).

In addition to kanamycin, capreomycin is also frequently administered intravenously. This is because capreomycin is a cyclic polypeptide with a different chemical makeup that results in less cross-resistance. It is utilized in cases

where resistance to all aminoglycoside antibiotics develops. In contrast to kanamycin, capreomycin has a low efficacy rate of 48% and a high mortality rate of 23%. In comparison to other injectable medications such as kanamycin, capreomycin exhibits decreased efficacy. When capreomycin is used, negative consequences (unfavorable outcomes) happen. (Cegielski et al. 2015). Capreomycin is the main therapy choice when there is a history of failure in treatment.

This study also illustrates the same profile from the use of kanamycin and capreomycin. The therapeutic effect in this study was seen based on the conversion time of ARB Sputum. Based on that, it can be seen that the majority of patients experienced conversion within 1–2 months. These results are also in line with other studies which showed that the majority of ARB sputum conversion occurs in less than 2 months (Khan et al. 2019; Soeroto et al. 2021). Most of the patients' ARB conversion times met the standards set in the drug-resistant tuberculosis treatment guidelines. The target time for ARB conversion to be negative within 2 consecutive months is 85%. If the conversion time is more than 2 months, this may occur due to patient factors such as the patient feeling cured and ultimately stopping treatment, thus, causing the patient to fall into the treatment failure category. Besides that, it could be due to the patient's lack of knowledge about the hazards of drug-resistant tuberculosis and the side effects experienced so the patient felt uncomfortable with the treatment (Kim et al. 2010). Therefore, it is necessary to provide education or counseling to patients about the importance of completing each stage of drug-resistant tuberculosis treatment (Cegielski et al. 2021).

Results of the Chi-square showed that there was no significant correlation between the type of injection and the achievement of therapeutic effect (p-value = 0.983). This shows that the use of kanamycin and capreomycin provides similar efficacy in drug-resistant tuberculosis. Most of the ARB sputum conversion occurred in the first and second months of treatment with kanamycin injection. These results are in line with those of other studies which demonstrated that the number of patients that had good response when using kanamycin was greater than capreomycin (2675 vs 1175 from 10560 patients). However, the mortality rate from capreomycin was higher than kanamycin (528 vs 547 of 10560 patients). A comparison of the efficacy of kanamycin and capreomycin showed no difference (OR of 0.8 [95% CI, 0.6–1.0]). Monitoring the treatment of drug-resistant tuberculosis has been going well, thus supporting medication compliance. Compliance with taking this medication is one of the main factors in the success of drug-resistant tuberculosis therapy.

The use of kanamycin and capreomycin injections can cause several side effects as is also the case with the use of oral anti-tuberculosis administered in drug-resistant tuberculosis. After therapeutic effectiveness is achieved with injection, drug-resistant tuberculosis treatment is continued using oral medication. Kanamycin and capreomycin have the potential to cause electrolyte disturbances, such as uric acid (Soeroto et al. 2019; Zulkarnain et al. 2023). It can be seen from the results of laboratory examinations that many uric acid values are abnormal. In addition, longer duration of anti-tuberculosis drug use can lead to decreased hematocrit (Kassa et al. 2016). The use of isoniazid also has the potential to cause hematological disorders (Sen et al. 1989; Minardi et al. 2021).

Interestingly, the present study also demonstrated that some patients had increased uric acid levels. This situation is to be related to the aminoglycoside-causing nephrotoxicity drugs such as kanamycin. The increased uric acid, known as hyperuricemia, has been studied to show that hyperuricemia is associated with the incidence of kidney disease. Monosodium urate crystals can cause nephrolithiasis and can also cause deposition of intraluminal microcrystals in collecting ducts. Urate can stimulate inflammatory agents and release interleukin-1beta with the impact of tubular injury and albuminuria. The results can result in a high risk of intrarenal inflammation, interstitial fibrosis, and even chronic kidney disease. Thus, hyperuricemia can be a sign or risk factor for kidney disease (Ponticelli et al. 2020).

Aminoglycosides have been reported to cause many ADRs in the form of nephrotoxicity and ototoxicity. Aminoglycosides cause accumulation in the proximal renal tubule which causes aminoglycoside levels in the blood to increase beyond the minimum toxic level. Another study showed that of 900 drug-resistant tuberculosis patients, there was a 6.7% incidence of nephrotoxicity (Shibeshi et al. 2019). Apart from that, kanamycin, which is an aminoglycoside, also has the potential to cause nephrotoxicity. From the results of other studies, it can be seen that of the 42 patients who used kanamycin, 7 of them experienced nephrotoxicity (Perumal et al. 2018).

Besides that, several results explain that increased uric acid can be caused by the use of oral anti-tuberculosis as a continuation of drug-resistant tuberculosis therapy (Septyani et al. 2020). The use of oral medications other than injections also contributes greatly to the risk of side effects. Thus, the combination of pyrazinamide and ethambutol can also increase the risk of hyperuricemia compared to a single administration of pyrazinamide or ethambutol. Pyrazinamide and ethambutol cause ion exchange in the renal tubules which causes excessive reabsorption of uric acid, leading to hyperuricemia, and if the two drugs are used together the effects are greater (Pham et al. 2014; Muhammad et al. 2021; Emorinken and Ugheoke 2022; Shin et al. 2023).

Many factors can influence the achievement of the therapeutic effect of a drug such as age, gender, length of therapy, and others. Several studies have shown that age affects the therapeutic effect of medication. In this respect, drug metabolism is particularly affected by physiological conditions in infants and elderly, leading to stronger and longer drug effects in these two age groups (Khan et al. 2019; Butov et al. 2020; Soeroto et al. 2021). The longer therapy duration and the higher number of medications might lead to the lower possibility of therapeutic effectiveness, thus understanding the importance of drug

compliance during long-term drug-resistant tuberculosis treatment is essential (Khan et al. 2019).

Conclusion

In conclusion, the results of the present study show that good therapy effectiveness for drug-resistant tuberculosis can be achieved with injection therapy, however, this should be accompanied by close monitoring particularly in patients who continue with oral treatment to avoid irreversible side effects. There was no relationship between age, gender, duration of therapy, and the amount of oral medication with the achievement of a therapeutic effect.

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