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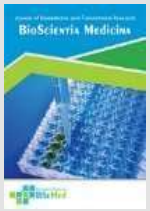

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Management of Isoniazid Monoresistant Tuberculosis

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A B S T R A C T

Isoniazid (INH) is one of the main first-line drugs used for the treatment of active tuberculosis (TB) and latent TB infection because it has bactericidal capabilities and a good level of safety. The presence of TB germs that are resistant to INH will reduce the effectiveness of TB treatment. The treatment mix for INH monoresistant TB patients is a combination of rifampicin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E), and levofloxacin (Lfx) or R-H-Z-E-Lfx given for 6 months. If a health facility provides loose TB medication, the patient can be given a combination of treatment without INH (R-Z-E-Lfx). In conditions where the Lfx drug cannot be used because there is severe intolerance (serious adverse events) or there are contra indications, the treatment given is the R-H-Z-E combination for 6 months. Clinical monitoring for patients with INH monoresistant TB follows the same principles as treatment of drug-sensitive TB. In conclusion, the treatment guide for INH monoresistant TB patients is a combination of rifampicin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E), and levofloxacin (Lfx) or R-H-Z-E-Lfx for 6 months.

1. Introduction

Tuberculosis (TB) is a directly infectious disease that is still a world health problem both in terms of morbidity and mortality. The reported global number of people newly diagnosed with TB was 7.5 million in 2022. This is the highest number since WHO began monitoring TB globally in 1995, surpassing the pre-COVID-19 baseline (and previous historical peak) of 7. 1 million in 2019, and increased from 5.8 million in 2020 and 6.4 million in 2021.[1,2]

Isoniazid (INH) is one of the main first-line drugs used for the treatment of active TB and latent TB infection because it has bactericidal capabilities and a good level of safety. The presence of TB germs that are resistant to INH will reduce the effectiveness of TB treatment. In 2018, WHO estimated the number of INH monoresistant TB cases at 7.4% in new TB and 11.4% in re-treatment TB. INH monoresistant TB is associated with an increased risk of acquired drug resistance and progression to MDR TB. There is still very little attention to INH monoresistant TB, although various studies show that the treatment failure rate in INH monoresistant TB is higher than in drug-sensitive TB.[3-5] This literature study aims to describe the management of INH monoresistant TB.

INH monoresistant TB

INH monoresistant TB is TB that is single-resistant to INH. Indonesia is a country included in the "high burden countries". It is estimated that around 8% of

TB patients worldwide have rifampicin-susceptible and isoniazid-resistant TB. In 2018, WHO estimated the number of INH monoresistant TB cases at 7.4% in new TB and 11.4% in re-treatment TB. INH monoresistant TB is associated with an increased risk of acquired drug resistance and progression to MDR TB.[6,7]

There are several diagnostic techniques to detect drug resistance, including drug susceptibility testing (DST) and fast molecular DST that detects specific DNA mutations in the genome *Mycobacterium tuberculosis*.[8] Optimal use of currently available tests is important for accurate diagnosis of INH-resistant TB, especially in countries with a high TB burden where diagnostic testing is limited. Further development of more rapid and accurate testing techniques for detecting resistance to INH is still needed.[7]

Guide to INH monoresistant TB treatment in Indonesia

INH is one of the main drugs in the treatment of TB.[9,10] In patients with INH monoresistant TB, ideally INH drugs should no longer be given in the treatment mix.[11] However, considering that the drug package provided by the National TB Program in Indonesia is a fixed-dose combination (FDC), INH drugs are still given in the treatment of INH monoresistant TB patients.[12,13]

The treatment mix for INH monoresistant TB patients is a combination of rifampicin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E), and levofloxacin (Lfx) or R-H-Z-E-Lfx given for 6 months. If a health facility provides loose TB medication, the patient can be given a combination of treatments without INH (R-Z-E-Lfx). In conditions where the Lfx drug cannot be used because there is severe intolerance (serious adverse events) or there are contraindications, the treatment given is the R-H-Z-E combination for 6 months.[13] Conditions under which INH monoresistant TB treatment can be given without levofloxacin include severe tendinitis, prolongation of the qt interval leading to fatal dysrhythmias, severe insomnia, and severe nausea and vomiting.

If Lfx cannot be used to treat INH monoresistant TB, administration of high doses of INH in the R-H-Z-E combination can be considered if it is known that the patient is experiencing low-dose INH resistance (inhA gene mutation), and if high-dose INH drugs are available. INH monoresistant TB patients who will be given high doses of INH need to be referred to a drug-resistant TB (RO) health facility. Aminoglycoside injection drugs (streptomycin, kanamycin, amikacin) and capreomycin should not be added to the treatment mix for INH monoresistant TB. All drugs in the INH monoresistant TB treatment are given every day for 6 months.

Extending the duration of INH Monoresistant TB treatment to 9-12 months can be considered in certain cases such as extensive lesion pulmonary TB, miliary TB, late converting pulmonary TB, and severe extrapulmonary TB. It should be noted that prolonging the duration of treatment may increase the risk of toxicity. INH monoresistant TB drugs are given according to the dosage based on the patient's weight group. Table 1 shows the OAT dose based on body weight for a combination of INH monoresistant TB treatment using FDC and loose-release drugs.[13]

Table 1. OAT dose based on body weight group for the fixed-dose group (FDC).

Body weight (kg)	RHZE (150/75/400/275 mg)	Levofloksasin (250 mg)
30- 37 kg	2 tablets 4 FDC	3 tablets
38- 54 kg	3 tablets 4 FDC	4 tablets
55- 70 kg	4 tablets 4 FDC	4 tablets
>71kg	5 tablets 4 FDC	4 tablets

Treatment of INH monoresistant TB in special conditions

Extrapulmonary TB

The R-H-Z-E-Lfx treatment combination can also be given to extra-pulmonary INH monoresistant TB patients based on consultation with the relevant specialist doctor. In extrapulmonary INH monoresistant TB, the duration of treatment is extended to 9-12 months.[11]

Liver disorders

Of all the first-line OAT used in the treatment of INH monoresistant TB, the drugs that have hepatotoxic effects are Rifampicin and PZA. In some literature, PZA has the most hepatotoxic effect. For patients with acute hepatitis and/or clinical jaundice, OAT that is hepatotoxic (namely Rifampicin and PZA) can be postponed until the acute hepatitis has healed. In cases of severe TB, a less hepatotoxic combination, namely ethambutol fluoroquinolone and streptomycin, can be temporarily given. After the situation improves, give the standard mixture from the start or continue from the previous mixture.[14,15]

In patients with advanced chronic liver disease, a complete liver function examination should be performed before treatment is initiated and periodically during treatment. If SGOT and/or SGPT levels are > 3x normal and/or total bilirubin > 2 mg/in before therapy is started then the following drug combination needs to be considered. The combination of drugs that can be given can contain 2 hepatotoxic drugs (R-Z-E-Lfx), 1 hepatotoxic drug (R-E-Lfx or Z-E-Lfx-S), or no hepatotoxic drug (S-E-Lfx).

Complete liver function monitoring must be carried out on all patients with hepatitis cirrhosis (chronic liver disease) every month because liver injury due to OAT is more common in patients who suffer from hepatitis cirrhosis (chronic liver disease) than in patients who do not and treatment can be changed based on liver function values. In cases of TB with comorbid liver disorders, it is recommended to be treated together with a gastroenterohepatology consultant.[14,15]

Pregnancy with TB

TB is associated with increased complications in pregnant women and babies. Delays in TB diagnosis and treatment will result in unfavorable outcomes. Inadequate TB treatment in pregnant women can cause complications such as preeclampsia, vaginal bleeding, miscarriage, premature labor and death. Changes in drug pharmacokinetics in relation to absorption, distribution, metabolism, and excretion during pregnancy are caused by physiological changes in pregnant women such as decreased gastric motility, changes in metabolic enzyme activity, increased activity of renal uptake/efflux transporters (causing increased renal clearance), increased total body fluids and blood volume, changes in cardiac output and decreased drug concentration due to reduced binding to albumin.[16,17]

According to the guidelines provided by WHO, first-line anti-TB agents can be used during pregnancy after considering the risks and benefits of treatment. WHO recommends that TB treatment in pregnant women should be the same as treatment in non-pregnant women, the only exception being that streptomycin should be avoided in pregnancy because it is ototoxic to the fetus. An increased incidence of abnormalities was not seen in infants of mothers treated with fluoroquinolones. However, animal studies of ciprofloxacin indicate a potential risk of articular cartilage damage when exposed to high doses. In general, fluoroquinolones can be used safely in pregnant women with drug-resistant TB where the benefits of treatment clearly outweigh the potential risks.[17]

TB in breastfeeding mothers

TB treatment is not considered a contraindication for a mother to breastfeed her baby. The concentration of TB drugs excreted into breast milk is so low that it cannot be used to treat babies. Breastfed infants may receive as much as 20% of the therapeutic infant dose of INH, while other antituberculous drugs are excreted to a lesser extent. No toxicity has been reported from these small concentrations in breast milk. However,

caution should be exercised as breast milk doses may contribute to increased plasma drug levels in newborns taking antituberculous drugs. To minimize this possibility, mothers can take the medicine immediately after breastfeeding.

If a baby requires treatment for active TB disease or as a primary prophylactic treatment, the drug dosage is based on body weight according to guidelines. Administration of pyridoxine is not considered necessary in breastfed infants of mothers receiving isoniazid unless the infant is also receiving isoniazid, but standard multivitamin supplementation should be considered. Breastfeeding is not recommended for mothers who have not started treatment at the time of delivery and for those who are still actively expelling germs when coughing. Babies of mothers with active TB can still be infected, through aerosol spread, even if fed formula. Therefore, if a mother is newly diagnosed with active TB and has not been treated, it should be separated from her baby to prevent exposure.[16]

HIV

ARV treatment is started within 8 weeks of starting TB treatment (regardless of CD4 count) or within 2 weeks in patients with obvious immunosuppression (eg CD4 count <50 cells/mm^3).[11,18]

Kidney disorders

Excretion of ethambutol and pyrazinamide metabolites occurs in the kidneys so it is necessary to adjust the dose or administration interval. The OAT dose for patients with renal failure is adjusted to the condition of the patient undergoing hemodialysis, creatinine clearance < 30 ml/minute, and peritoneal dialysis. If creatinine clearance is <30 ml/minute, the rifampicin dose is not affected, so there is no need to change the dose. Ethambutol, pyrazinamide, and levofloxacin are fixed doses but the frequency of administration is 3x a week and OAT is given directly after dialysis.[11]

Initiation of INH monoresistant TB treatment

TB patients with sensitive rifampicin TCM results with a history of previous treatment can be immediately given TB treatment with the R-H-Z-E combination while waiting for the results of the INH and levofloxacin sensitivity test. The results of the INH and levofloxacin susceptibility test must be available within 1 week so that the treatment regimen can be adjusted immediately. If the susceptibility test shows resistance to INH but sensitivity to levofloxacin, then the TB treatment status is closed and recorded as "failed due to change in diagnosis". The patient was re-registered as an INH Monoresistant TB patient and R-H-Z-E-Lfx treatment was started from the beginning. The drug levofloxacin cannot be given until the results of the sensitivity test (LPA) are available and the sensitivity is known.[9]

If the results of first-line LPA show rifampin resistance, even though the TCM results show rifampin sensitivity, then the patient is managed as an RR/MDR TB patient. The discordance between first-line LPA and TCM may occur due to differences in the gene targets examined. If the patient's diagnosis is based on a strong suspicion of INH Monoresistant TB, namely close contact with a patient with confirmed INH Monoresistant TB, treatment of INH Monoresistant TB with the R-H-Z-E-Lfx combination can be started immediately even though the results of the INH and Lfx susceptibility tests are not yet available. Treatment may be adjusted if sensitivity test results are available.[11,19]

Treatment monitoring

Clinical monitoring for INH monoresistant TB patients follows the same principles as treatment of drug-sensitive TB (TB SO). Bacteriological monitoring also follows the same schedule as TB SO, where BTA examinations are carried out at the end of the 2nd month, the end of the 5th month, and the end of treatment. In patients who do not respond to treatment (if the BTA results are still positive at the 2nd, 5th, 6th month), it is necessary to undergo a repeat TCM MTB/RIF examination. Supporting

examinations for monitoring the treatment of INH Monoresistant TB patients are different from TB SO patients.[13]

Table 2. Monitoring treatment of INH monoresistant TB patients.

No	Checking type	Information
Physical examination		
1	Vital signs	First 2 months: every 2 weeks; (4x) Next 4 months: every month; (4x) unless the patient experiences an adverse event.
2	General physical examination	First 2 months: every 2 weeks; Next 4 months: every month; unless the patient experiences an adverse event.
Microbiological examination		
1	BTA sputum	2nd, 5th, 6th month.
2	Sputum sensitivity test	TCM MTB/RIF is repeated if the BTA examination results are still positive at months 2, 5, and 6; If the Rif result is resistant, then patient management follows the TBC-RR/TBC RO pathway.
Supporting investigation		
1	Vision test	Repeated when indicated.
2	HIV testing	Repeated when indicated.
3	Liver function: SGPT, SGOT	According to indications.
4	Kidney function; creatinine, urea	According to indications.
5	ECG	According to indications.
6	Chest X-ray	Repeated at 2 and 6 months if facilities are available.

Management of active drug side effects and treatment outcomes of INH monoresistant TB

In patients who experience an itchy reaction without redness and there is no other cause, the recommended treatment is symptomatic medication. Treatment can be continued by observing the patient. If redness occurs on the skin, OAT must be stopped. If the reaction has reduced and healed, OAT can be tried one by one, starting with OAT which rarely causes allergic reactions.[12,13]

If during the reintroduction process, a drug is found that causes allergies, then the drug must be stopped. The drug desensitization process is an option that can be taken, especially if the patient is allergic to first-line and second-line drugs or if there are no other better options. Drug desensitization is contraindicated in hypersensitivity reactions that are not mediated by lgE, for example in Steven-Johnson Syndrome reactions.

The drug desensitization process is carried out depending on the severity of the allergic reaction that occurs. If the allergic reaction is mild, desensitization can be carried out with a single-step daily escalation. If the allergic reaction you experience is severe, you can start with a much smaller dose and increase it gradually several times a day (multistep daily dose escalation).[11,12] The final results of INH monoresistant TB treatment are the same as SO TB and can be seen in Table 3.

Table 3. Final results of INH monoresistant TB treatment.

Treatment results	Definition
Healed	Pulmonary TB patients with positive bacteriological examination results at the start of treatment whose bacteriological examination results at the end of treatment are negative and one of the previous examinations.
Complete treatment	TB patients who have completed complete treatment where one of the examinations before the end of treatment was negative but without any evidence of bacteriological examination results at the end of treatment.
Failed	For patients whose sputum examination results remain positive or return positive in the fifth month or more during the treatment period; or at any time during the treatment period laboratory results are obtained indicating OAT resistance.
Died	TB patients who died from any cause before starting or being treated.
Dropped out of treatment	TB patients who do not start treatment or whose treatment is continuously interrupted for 2 months or more.
Not evaluated	TB patients whose final results of treatment are unknown. Included in these criteria is transfer out to another district/city where the final results of the treatment are not known to the remaining district/city.

2. Conclusion

The treatment guide for INH monoresistant TB patients is a combination of the drugs rifampicin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E), and levofloxacin (Lfx) or R-H-Z-E-Lfx given for 6 months.

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