Effectiveness and Safety of Shorter-Term Regimen (STR) for Multidrug-Resistant Tuberculosis (MDR-TB) Treatment: A Systematic Review of Cohort Studies

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ABSTRACT

The multidrug-resistant tuberculosis (MDR-TB) remains a significant public health burden in term of the successful TB treatment because of the lack awareness of TB drugs administration. Patients infected with MDR-TB are resistant to isoniazid (INH) and rifampicin (RMP) due to genotypic mutation, thus could not adequately treated by the first-line regimen standards. The management of MDR-TB using Short-Term Regimen (STR) is a crucial topic to be discussed due to low success rate of conventional therapy and its long duration. This systematic review aims to further examine the effectiveness and safety of STR to manage MDR-TB. In this systematic review, various cohort studies were searched using standardized Preferred Reporting

Items for Systematic Reviews and Meta-Analyzes (PRISMA). The keywords were arranged based on Problem, Intervention, Comparison, and Outcome (PICO). Key terms consisted of multidrug-resistant tuberculosis and short regimen therapy. Seven cohort studies were selected from 314 studies. STR has better therapeutic efficacy and shorter duration than the 2011 WHO regimen for MDR-TB with therapy success rates for each study above 50%. The most effective regimen according to studies in this review is kanamycin-high dose isoniazid-clofazimine-ethambutol-prothionamide-pyrazinamide-gatifloxacin (KM-INH-CFZ-EMB-PTH-PZA-GFX) in the intensive phase for 4 months and clofazimine-ethambutol-pyrazinamide-gatifloxacin-prothionamide (CFZ-EMB-PZA-GFX-PTH) in the continuation phase for 8 months. The four most reported side effects were gastrointestinal problems, ototoxicity, dysglycemia, and liver problems. In conclusion, STR provides good effectiveness in MDR-TB treatment, in terms of treatment success rate and short therapy duration. Therapy with STR is relatively safe, with minimal side effects that can be tolerated in the majority of individuals.

Keywords: Multidrug-Resistant Tuberculosis, short term regimen, safety, adverse drug effect, effectivity.

INTRODUCTION

Antimicrobial resistance is still a worrying worldwide public health issue due to the high cost of medical treatment and the potentially severe repercussions it causes.[1] This antimicrobial resistance occurs when the microorganism has an adaptive response when exposed to antimicrobial treatment.[1,2] One of the cases of emerging antimicrobial resistance is multidrug-resistant tuberculosis (MDR-TB). According to the World Health Organization (WHO), there were 480,000 new cases of MDR-TB in 2014, with

only half of them successfully treated. Furthermore, only a quarter of all MDR-TB cases were estimated to be detected and reported in health facilities.[1] In Indonesia, the incidence of MDR-TB was 24,000 out of 845,000 total cases of TB, with the estimated number of new cases being 2.4% in 2018.[3]

MDR-TB is one of the most crucial and problematic challenges in facing global TB treatment.[4] Patients infected by MDR-TB are resistant to isoniazid and rifampicin due to genotypic mutation, thus proven incurable by standard first-line treatment.[1-4] The main factors that cause the increasing numbers of MDR-TB cases include inadequate medical monitoring systems, the incorrect treatment which could change resistance patterns, and community-based transmission.[4] Moreover, in terms of therapeutic effectiveness, the success rate of MDR-TB treatment using the second-line treatment in Indonesia was only 48% with a relatively high frequency of a relapse.[3,5] WHO recommends 20 months for the total MDR-TB therapy duration, but the success rate of said treatment is still relatively low, which does not exceed 50%.[5] The recommendation of second-line treatment based on WHO guidelines in 2011 are fluoroquinolone (FQ), ethionamide (ETH) or protionamide (PTH), and cycloserine or para-aminosalicylic acid, with the addition of pyrazinamide (PZA) for a total duration of 20 months.[6] The duration of the treatment will affect the compliance of the patients, therefore influencing the entirety of the course.

In this situation, an attempt of using the Short-Term Regimen (STR) to face the MDR-TB crisis as an alternate method proves to be promising.[7,8] The Short-Term Regimen is a treatment for MDR-TB that could effectively reduce the duration of drug administration. STR is summarized into three drug classes, including FQ (ofloxacin,

gatifloxacin, moxifloxacin, etc.), core drugs (kanamycin, prothionamide, etc.), and active companion drugs (clofazimine and first-line drugs such as isoniazid, etc.).[9]

The therapy of MDR-TB using STR is crucial and essential to explore, as it has the potential to increase the success rate of MDR-TB treatment. Since the invention of the Bangladesh regimen in 2010, which only required nine months of treatment, several studies have also carried out to implement a similar regimen in MDR-TB management.[9,10] Several new regimens have also been reported to possess comparative effectiveness with long-term regimens.[11,12]

Related to the emerging various STR in the past decade, an update on the application of STR in the management of MDR-TB is needed to increase the success rate of MDR-TB therapy. Therefore, this systematic review aims to further examine the effectiveness and safety of various STR to manage MDR-TB. In addition, this study will also discuss several issues related to the possibility of implementing the results in the form of cost-analysis and its comparison with some of the recommendations for the management of pre-existing MDR-TB. In the end, this systematic study is expected to contribute to the more effective and safer management of MDR-TB in the community for the future.

METHODS

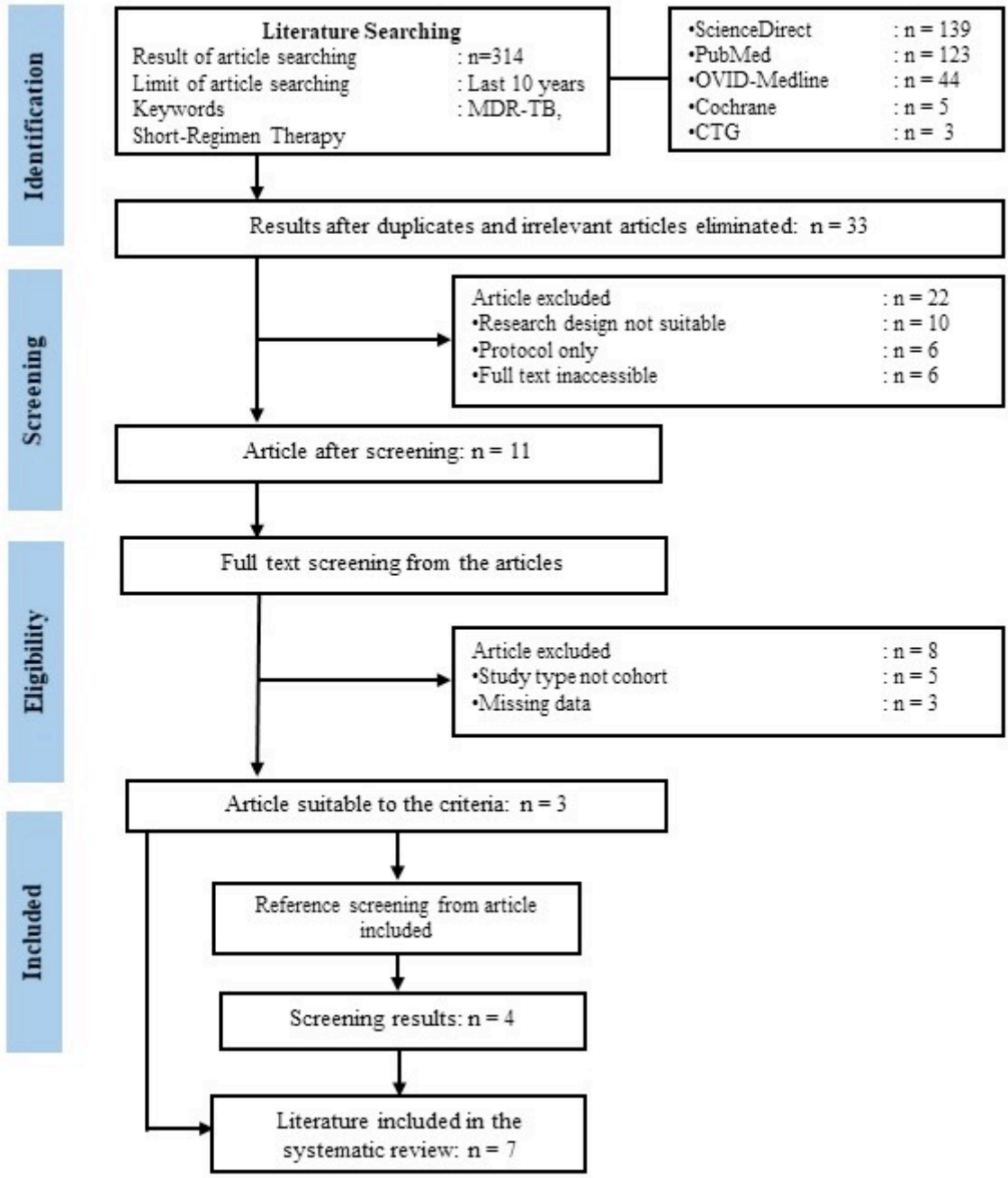
This Systematic Review was constructed according to the rules of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA), which evaluated the effectiveness and safety of STR as an MDR-TB treatment. The writing of this report reviewed the effectiveness and safety of STR by comparing Population, Intervention, Control and Outcome (PICO) data. The PICO answers from this

systematic review are, respectively, patients diagnosed with MDR-TB; STR was defined as the administration of several drug combinations and FLQ options for the duration of 6-12 months; standard of recommended therapy regimens published by WHO in 2011; review of the effectiveness and adverse effects of STR.

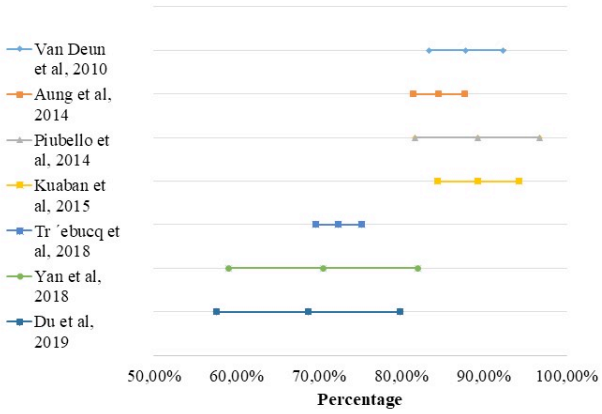
Data sources were traced through several search engines, including ScienceDirect, PubMed, OVID-Medline, Cochrane, and Clinicaltrials.gov (CTG). Article tracing was done to identify studies and research published in medical journals for the last ten years from January 2009 to December 2019, which focused on studies related to MDR-TB and the management. The keywords were arranged based on PICO by utilizing Boolean searching and truncation to expand the area of inquiry, consists of 'multidrug-resistant tuberculosis' or 'MDR-TB' and 'short regimen' or 'short-term regimen' or 'short course regimen'..The searching limitations which were applied through search engines included: the type of article, the search period, and the year of the published article.

The inclusion criteria were 1) Patients in all age groups diagnosed with MDR-TB; 2) The studies which included STR with a duration of therapy of 6-12 months; 3) The studies which included the effectiveness and adverse effects of STR; 4) Clinical studies which were published between January 2009 to December 2019; 5) Full-text articles published in English. Meanwhile, the exclusion criteria were the studies that did not meet the inclusion criteria, systematic reviews, and other meta-analysis articles. The specific keywords were used to generate chosen articles based on abstracts and full text. The selection of data sources referred to the inclusion criteria that were previously determined. After that, all abstracts and full texts were downloaded and evaluated

respectively. All complete texts that met the inclusion criteria were read independently by the authors and evaluated to formulate a systematic review **(Figure 1).**



Authors	Successful Therapy (95% CI)
Van Deun et al, 2010	87.80 (83.34-92.26)
Aung et al, 2014	84.50 (82.38-87.26)
Piubello et al, 2014	89.20 (81.65-96.75)
Kuaban et al, 2015	89.30 (84.36-94.24)
Tr ´ebucq et al, 2018	72.40 (69.64-75.16)
Yan et al, 2018	70.50 (59.06-81.94)
Du et al, 2019	68.70 (57.60-79.80)



RESULTS AND DISCUSSION

At the beginning of the literature searching, there was a total of 314 studies found. Furthermore, there were also four additional studies included that were filtered from the reference list of articles used. After excluding irrelevant articles and duplicates, 33 studies were found. The remaining 11 studies were then analyzed based on exclusion criteria, such as the type of study and the completeness of the data.

After applying the inclusion criteria, seven studies published between 2010-2019 were obtained. Then, the risk of bias was analyzed using the Newcastle-Ottawa scale. The results of the study analysis can be seen in Appendix 1. Every included study was a prospective cohort taken from different countries, such as Bangladesh, Nigeria, Cameroon, nine countries in Africa, and China.[5,9–15]

The datas that were used in those studies came from clinical trials performed between 1997 – 2016, with detailed explanation as follows: two studies ranged two years,[5,10] one study ranged three years,[14] one study ranged four years,[12] two studies ranged six years,[11,13] and one study ranged ten years.[9] From the total of seven studies,

there were two studies which compared STR with long term therapy (LTR),[11,12] while the five other studies only explained about STR.[5,9,10,13,14] The total subjects who were analysed in this systematic review numbered 2,157 patients from the age of 12 until 80 year old. The TB drug sensitivity which was analysed in early diagnosis of the patient for each study was the resistance to isoniazid (INH) as well as rifampin (RMP), and met the definition of MDR-TB.[5,9–14] Two other studies also diagnosed the resistance to fluoroquinolones (FLQ).[5,13] Human immunodeficiency virus (HIV) status was analysed in three studies, whereas the four other studies did not analyse HIV status due to the limitation of studies.[9,11–13] The characteristics of the studies are shown in **Table 1.**

Analysis of the Composition of STR

As the incidence of MDR-TB are increasing further, the TB drugs which used to be divided into two groups are now divided into five major groups. Group 1 consists of first-line oral drugs, such as rifabutin (RFB), ethambutol (EMB), and isoniazid (INH).[15] The type of INH used is high dose INH (INHh), with the considerations of being effective in patients with low-level resistance toward INH and is able to eradicate bacteria strain which also resistant to prothionamide (PTH). It was reported that some individuals with low-level resistance to INH have resistance to PTH.[5] Ethambutol is still used in the STR because of its effectiveness.[14] Rifabutin is also used as STR choice drug for MDR-TB because it has a higher affinity to bacterial RNA polymerase compared to rifampin.[11] In this systematic review, RFB was used in one regimen,[11] INHh in five regimens,[5,9,10,13,14] and EMB in five regimens. [5,9–11,13,14]

Group 2 consists of injectable agents, such as kanamycin (KM).[15] Kanamycin is often used in the STR because of its efficacy and affordability.[16] In this systematic review, KM is used in five regimens.[5,9,10,13,14]

Group 3 consists of FLQ and pyrazinamide (PZA).[15] Some FLQ options that were used in MDR-TB STR include gatifloxacin (GFX), moxifloxacin (MFX), and levofloxacin (LFX). The consideration of choosing FLQ is due to the effectiveness and possible resistance to FLQ in the future.[17] GFX was used in four regimens,[9,10,13,14] while MFX is in two regimens, [5,11] and LFX is in one regimen.[12] Furthermore, PZA is also used as a sterilizing drug with comparable efficacy to rifampin in increasing the effectiveness of fluoroquinolone (FLQ).[18] In this systematic review, PZA is used in each regimen.[5,9–14]

Group 4 consists of second-line TB drugs, including prothionamide (PTH), cycloserine (CS), and para-aminosalicylic acid, such as pasiniazid (PSD).[15] The PTH is a bactericidal agent used in STR due to its high efficacy.[19] The cycloserine has been used as an anti-TB agent since 1950, but it began to be abandoned after the discovery of better options, such as rifampicin.[20] PSD, a combination drug made from p-aminosalicylic acid and INH, is chosen for MDR-TB treatment because more than 80% of patients with resistance to INH still responded to PSD.[21] In this systematic review, PSD was used in one regimen,[11] CS in one regimen,[12] and PTH was used in six regimens.[5,9,10,12–14]

Group 5 consists of drugs whose efficacy had not been proven in MDR-TB, such as clofazimine (CFZ).[15] The clofazimine was used as an option in the STR because of its high effectiveness and tolerability as companion drugs.[20] In this systematic review, CFZ is used in six regimen.[5,9,10,12–14]

Overall, the STR in this systematic review consists of at least one anti-TB drug in group 1, one in group 2, PZA and one group of FLQ in group 3, one in group 4, and CFZ in group 5. Some reported regimens have exceptions, such as one regimen not using anti-TB drugs in group 1[11] and one regimen not using anti-TB drugs in group 5.[12] The regiments recommended by WHO in 2011 consisted of only three groups, including one anti-TB drug in group 2, PZA and one group of FLQ in group 3, and one in group 4. The effectiveness and safety of each regimen will be explained in the following subsections.

The effectiveness of STR in terms of success and duration of STR

Generally, STR have a better therapeutic effect and shorter duration than the 2011 WHO regimen for MDR-TB with treatment success rates above 50% for each studies.[6] There are four studies which had success rates above 80%[9,10,13,14] and three other studies below 80%.[5,11,12] One study that reported a success rate of <80% was due to the high mortality rate which was unrelated to the effectivity of STR, such as starvation and infected by HIV. In hindsight, the success rate of therapy in patients who survived was quite high, which was 88.9%.[5]

Likewise, two other studies with therapeutic success rates less than 80% have a smaller pool of samples which caused a wide range of confidence interval (CI). However, they have shown better therapeutic success rates compared to the LTR in each study, although with a fairly narrow difference (STR 70.5% and 68.7%, LTR 63.1% and 64.7%)[11,12] These two studies used regimens that were slightly different from others. One study with a 70.5% success rate used the STR with the shortest duration, which was five months, with the addition of pasiniazid (PSD) and rifabutin (RFB) instead of

isoniazid (INH) and rifampin in the management of normal TB.[11] The other study with a success rate of 68.7% used STR for a duration of 12 months with the addition of cycloserine (CS).[12]

According to a study conducted by Li in 2019, the single-drug administration of CS had a good outcome and proved to be safe with fewer adverse reaction compared to other anti-TB drugs.[20] RFB and PSD were also reported to have good efficacies, and the administration could reduce the risk of different MDR-TB strain transmission.[21,22] However, the concept of TB therapy is directed at the effectiveness of the regimen and not in the form of a individual drug administration.[23] Even though each of RFB, PSD, and CS have good potency, there is still a pressing need for the evidence of simultaneous drug use in one regimen to evaluate their efficacy in MDR-TB. In addition, there is still a lack of study regarding the efficacy of administrating similar regimen compared to the two studies mentioned previously.

There were three studies using the same regimen consisting of kanamycin (KM), high-dose isoniazid (INH), clofazimine (CFZ), ethambutol (EMB), prothionamide (PTH), pyrazinamide (PZA), gatifloxacin (GFX) in the intensive phase and CFZ, EMB, PZA, GFX in the continuation phase.[9,10,13] These aforementioned three studies reported a therapeutic success rate of more than 80%.[9,10,13] The duration of the three studies were slightly varied; two studies used four months intensive phase and five months intensive phase,[9,13] with similar success rates, being 87.8% and 84.5%, and the relapse rate after two years was quite low, which were 0.5% and 0.8% respectively.[9,13] Whereas, in the other two studies, the continuation phase had a longer duration compared to the three studies with a span of 8 months. This addition of three months duration gave a therapeutical success rate of 89.2%, and no relapse was reported after two years of

follow-up.[10] Other studies revealed the administration of similar regimens with the addition of eight months of PTH in the continuation phase, with a success rate of 89.3% and without relapse after two years.[14]

There are two studies that revealed the effectiveness of STR in patients with HIV comorbidity. The success rate of less than 80% was found in one study, which was likely due to high mortality in HIV patients. However, if the success rate of therapy was calculated from surviving HIV patients, the success rate of therapy reached 88.4%.[5] The other five studies did not include HIV patient due to the limitation of studies.[9–14]

Fluoroquinolone (FLQ) option in STR

The use of FLQ is essential in composing the STR for MDR-TB. The majority of studies used GFX as an FLQ option in STR.[9,10,13,14] One study replaced the FLQ from GFX to moxifloxacin (MFX) and had less than 80% success rate. This might occur due to the fact that in two years of therapy, 1.4% of total patients had a high-level resistance to FLQ.[5] STR which used LFX option also had less than 80% success rate. These results are supported by a study conducted by Van Deun in 2019, where the use of GFX had a higher effectiveness (97.5%) compared to LFX and MFX (95.5% and 94.7%) with a lower incidence of adverse effect. In addition, compared to GFX, patients with LFX and MFX had a tendency to form resistance to FLQ, which were respectively 4.5 and 8.4 times higher than GFX.[17]

The resistance to FLQ is an important aspect to consider in composing the STR. In one study, the FLQ resistant group had a quite successful therapeutic rate (70.96%), however, if it was classified into two groups of low-level resistance and high-level resistance, the high-level resistance group had a lower success rate (46.67%).[13] Similar

results were also reported in another study, with a therapeutical success rate of 59.2% in the group with FLQ resistance and 55.6% in the group with high-level resistance.[5] A literature review by Trebucq made a comparison of FLQ resistance development speed by FLQ besides GFX with rifampicin. The resistance development speed to rifampicin is 1 per 1000 after six months, whereas in FLQ other than GFX can reach up to 10-20 per 1000 patients.[23]

At this moment, the latest Indonesian recommendations for MDR-TB published in 2016 were still using the MFX option as FLQ.[22] The consideration to replace the FLQ option from MFX to GFX is needed to increase the effectiveness of MDR-TB therapy in the future. This substitution may require the role of WHO because this drug still cannot be purchased in some countries. Therefore, it needs to be included in the WHO Model List of Essential Medicines.[23]

Unsuccessful Treatment and Relapse in STR

The number of unsuccessful failed, and defaulted treatments, as well as the subjects that died afterward is parallely related to the success rate of each STR used. A study reported that the mortality rate was the main cause of therapy failure (9.2%), but this was mainly due to low BMI, old age, extensive pulmonary lesions, and HIV infection; thus not affecting the effectiveness of the overall regimen.[10] The relapse level was reported in four studies after two years of follow-up, with two studies reporting no relapse[10,14] and two other reported relapse rates below 1%.[9,13]

The STR safety in terms of side effects

Overall, the four most reported side effects were gastrointestinal problems, ototoxicity, dysglycemia, and liver problems. Five studies reported mostly gastrointestinal side effects (21.4%, 21.6%, 33.9%, 57.1%, and 3.0%).[5,9,10,12,13] This side effect was probably caused by the use of PTH in the continuation phase.[9,10] Another side effect was ototoxicity in five studies (6.3%, 1.4%, 20%, 16%, and 44.3%) which was caused by KM.[5,9,10,13,14] Dysglycemia occurred in three studies (3.9%, 1.5%, 9.2%) due to GFX.[9,10,13] Side effect in the liver was shown in three studies (6,6 %, 48.9%, 16.4%).[5,12,14]

Six studies reported a level of side effects less than 30%. In one study with a side effect level more than 30%, it was the result of calculation that factored mild to severe symptoms (from grade 1 to grade 5). However, the study explained that there need not the cessation of the treatment for the patient due to the side effects. Overall, there was only one study that had to stop therapy because of the side effects in two patients.[11] Excluding that, the other five studies reported no discontinuation of therapy due to the side effects found. However, some adjustments related to dosage and drug use are still made in several studies.[5,9–11,13,14]

Cost-Analysis STR

In seven cohort studies obtained to this study, it was found that STR could be used as the primary therapy for MDR TB patients with a high successful rate and a lower average cost. The average cost of each STR regimen were approximately: kanamycin 250 mg US $ 0.11, moxifloxacin 400 mg US $ 3.27, prothionamide 250 mg US $ 0.14, clofazimine 100 mg US $ 0.42, pyrazinamide 750 mg US $ 0.7, isoniazid 300 mg US $ 0.3, ethambutol 500 mg US $ 0.075, gatifloxacin 400 mg US $ 0.07,

rifabutin 150 mg US $ 11, cycloserine US $ 6.50, levofloxacin US $ 0.10. Compared to MDR TB therapy with the usual regimen and duration of therapy 18-24 months, it could be calculated a cost of US $ 4630,75/patient. The cost of using this STR is still superior compared to WHO's all-oral-regimen recommendations which currently range from US $ 6000.[23]

CONCLUSION

In general, STR provides better benefits in MDR-TB treatment, particularly in its effectiveness and the short duration of therapy. The STR is relatively safe, with minimal side effects that can be tolerated in most patients. The STR combination analyzed in this systematic review consisted of at least one anti-TB drug in group 1, one in group 2, PZA and one group of FLQ in group 3, one in group 4, and CFZ in group 5. The suggested option for FLQ group is GFX, considering the aspects of effectiveness, safety, and the resistance development to FLQ that might occur. The most effective regimen according to studies analyzed in this review is KM-INH-CFZ-EMB-PTH-PZA-GFX in the intensive phase for 4 months and CFZ-EMB-PZA-GFX-PTH in the continuation phase for 8 months. Based on the cost-analysis results, therapy with STR has a more affordable price compared to the WHO recommendation in 2011 and the WHO all-oral-regimen recommendation in 2019 for MDR-TB.

This systematic review has a limitation. There was no heterogeneity analysis of each study used. These limitations could open the opportunity to compile other meta-analyses to assess the heterogenity of the data and the formation of quantitative conclusions in the future. Further research into the success rate of several new STR is needed to assess the effectiveness in various other settings. It is also possible to perform

a study which could compare the effectiveness of the regimen composition in each anti-TB group to produce a safer STR, or other systematic review which evaluates RCT studies covering the same topic. The development of STR management for MDR-TB at this time is not infallible yet. However, with evidence in the form of further research on the STR management methods, an ideal treatment for MDR-TB might be discovered.

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