Outcomes of Daily Dose versus Part-daily Dose Treatment for Lung Tuberculosis: A Real-World Database Study in an Indonesian Hospital

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ABSTRAK

Latar belakang: *sebuah meta-analisis randomized controlled trials (RCTs) pengobatan tuberkulosis (TB) paru kategori I menyatakan bahwa paduan obat antituberkulosis (OAT) dosis berselang sebagian (2RHZE/4R3H3) dan dosis harian (2RHZE/4RH) mempunyai kegagalan dan kekambuhan yang sama banyaknya. Namun, World Health Organization (WHO) menyatakan bahwa paduan dosis berselang sebagian mempunyai kegagalan dan kekambuhan yang lebih tinggi. Penelitian ini dilakukan untuk membandingkan hasil pengobatan antara kedua paduan, apakah paduan dosis harian memberikan hasil pengobatan yang lebih baik daripada paduan dosis berselang sebagian, dan membandingkan efek samping kedua paduan tersebut.* ***Metode:*** *penelitian ini merupakan studi analitik cross-sectional di Rumah Sakit Umum Pusat (RSUP) Persahabatan periode Januari 2015-Juni 2018. Data diambil dari rekam medik dilengkapi wawancara per telepon dan setiap kelompok terdiri dari 175 pasien.* ***Hasil:*** *tidak ada perbedaan bermakna untuk keberhasilan pengobatan (p=0.470), putus berobat (p=0.659), gagal (p=1.000), meninggal (p=1.000), dan kejadian efek samping pada tahap lanjutan (p=0.324) di antara kedua kelompok. Namun, paduan dosis berselang sebagian lebih baik daripada paduan dosis harian dan berbeda bermakna untuk kesembuhan (p<0.001) dan pengobatan lengkap (p<0.001).* ***Kesimpulan:*** *kesembuhan dan pengobatan lengkap paduan dosis berselang sebagian lebih baik daripada paduan dosis harian. Keberhasilan pengobatan kedua paduan sesuai dengan target Indonesia (90%). Tidak ada perbedaan bermakna kejadian efek samping pada tahap lanjutan di antara kedua paduan.*

Kata kunci*: efek samping, paduan dosis berselang sebagian dan dosis harian, hasil pengobatan, tuberkulosis paru.*

ABSTRACT

Background*: a meta-analysis of randomized control trials (RCTs) on category I pulmonary tuberculosis (PTB) treatments showed that either part-daily (2RHZE/4R3H3) or daily dose (2RHZE/4RH) had the same failure and recurrence rates. However, the World Health Organization (WHO) concluded that the part-daily dose had higher failure and recurrence rates. Therefore, this study was conducted to compare the treatment outcomes between both regimens, whether daily dose regimen has a better treatment outcome than part-daily dose regimen, and the adverse effects between both regimens.* ***Methods:*** *this was an analytic cross-sectional study of patients at the Persahabatan General Hospital, over the period of January 2015-June 2018. Data were taken from medical records and supported by telephone interviews, each regimen group had 175 patients.*

Results: *there were no significant differences for success rates (p=0.470), lost to follow up rates (p=0.659), failure rates (p=1.000), death rates (p=1.000), and adverse effects in the continuation phase (p=0.324) between the groups. There were, however, significant differences in cure rates (p < 0.001) and complete treatment rates (p<0.001) between the groups.* ***Conclusion:*** *the cure rate and complete treatment rate were found to be better for the part-daily than the daily doses. The success rate of both regimens were the same as Indonesia's target (90%). In the continuation phase, there were no significant difference of adverse effects between both regimens.*

Keywords*: adverse effects, part daily and daily dose regimen, treatment outcomes, pulmonary tuberculosis.*

INRODUCTION

Indonesia ranks third as a country with the highest prevalence of tuberculosis (TB).[1] From 2008-2017, the success rates of treatment in Indonesia decreased (89.5% to 85.7%) to become lower than the target (90%).[2] Non-compliance was one major cause of treatment failure due to, among others, inconvenience to consume drugs daily, long duration of treatment, and the emergence of side effects.[3,4]

Since 2008, the WHO has recommended the daily dose regimen for category I TB treatment, which is divided into intensive phase for two months [rifampicin (R), isoniazid (H), ethambutol (E), and pyrazinamide (Z)], and the continuation phase for four months (R and H). The part-daily dose is an option if patients can be supervised closely to make sure that drugs are taken routinely, or if the patients do not have HIV or other comorbidities which might interfere the antituberculosis drugs (ATD) absorption.[5-7]

Since 2017, the WHO stated that part-daily dose had a higher rate of treatment failure and recurrence as compared to the daily dose.[7] However, the Ministry of Health of the Republic of Indonesia still recommend both regimens for pulmonary TB (PTB) treatment.[5]

A study conducted in South Sulawesi (2008) using a part-daily dose showed good outcomes.[8] A meta-analysis of RCTs (2017) indicated that both regimens had the same proportion of failure, recurrence, and resistance rate.[6] Both studies contradicted to the WHO's statement above.

Therefore, referring to the WHO statement above, this study was conducted to compare the real-world data of the treatment outcomes between both regimens, whether daily dose regimen has a better treatment outcome than part-daily dose regimen, and the adverse effects between both regimens. The results could be useful real world evidence for TB treatment in Indonesia.

METHODS

This was an analytic cross-sectional study using hospital database and supported by telephone interviews, whenever needed, at the Persahabatan General Hospital-a national reference TB treatment hospital in Indonesia. With an α value of 5% and research power of 80%, the minimum sample size for each group was 175 patients. All eligible outpatient and inpatient within the period of January 2015 - June 2018 were included in the first step of recruitment. They were newly diagnosed bacteriologically confirmed or clinically Pulmonary TB and age ≥ 18 years, who used part-daily or daily doses of ATD. In the intensive phase for two months, all patients received treatment daily, while in the continuation phase for four months they received either daily or thrice weekly treatment. The exclusion criteria were pregnant patients, impaired kidney function, liver disease, multidrug-resistant TB and extensive drug-resistant TB, TB with HIV or diabetes mellitus, and patients whose evaluations were not noted in the medical records. Only 350 medical records taken consecutively starting from January 2015, that satisfied the inclusion and exclusion criterias, were included in the study. Evaluation of treatment outcomes, adverse effects, and recurrence were performed according to definitions in the WHO and Indonesia's TB management guidelines.

The collected data was analyzed using SPSS (version 20.0). We used chi-square statistical test, and additional the Fisher's exact test as needed. This study was approved by the research ethics committees at the Persahabatan General Hospital and the Faculty of Medicine Universitas Indonesia (reference number 72/

KEPK–RSUPP/12/2018 and 1126/UN2.F1/ETIK/2018).

RESULTS

From 1364 medical records of TB patients which taken from January 2015 - June 2018, consecutive sampling was done to reach the needed sample size of total 350 medical records which satisfied the inclusion and the exclusion criterias (175 for each group). Data taken from medical records were patient identity, body weight, clinical symptoms, diagnosis, comorbid, duration of treatment, results of sputum bacteriological examination (acid fast bacteria/AFB microscopic, culture, and genexpert), radiological findings, and adverse effects. Data taken from telephone interviews was whether they experience any recurrence of TB during the period covered by this study (2015-June 2018).

General and Clinical Characteristics

The majority of patients were diagnosed as clinically PTB (53.1%). Most patients in the part-daily dose group were diagnosed as bacteriologically confirmed PTB (61.7%), while in the daily dose group most were diagnosed as clinically PTB (68%). The cough disappeared within ≤ 8 weeks of treatment (60,5%). Most patients in both groups had gained weight following treatment completion (86%) (**Table 1**) and this mainly occurred during the intensive phase (64.1%).

Treatment Outcomes

The cure rate (cure is define as sputum conversion from positive to negative) was significantly higher in the part-daily dose group (39.4% vs. 13.1%, prevalence ratio or PR 3.000). The complete treatment rate was significantly lower in part-daily dose group (52% vs. 76%, PR 0.684). The results for the other treatment outcomes are shown in **Table 2**. The proportion of bacteriological PTB patients with complete treatment whose cough disappeared in ≤ 8 weeks treatment was much higher in the daily dose group (70.8% vs. 46.4%).

Safety and Recurrence

In the continuation phase, there were 42 patients (12%) who had adverse effects. It was

Table 1. Patients Characteristics

General and clinical characteristics	Daily dose (2RHZE/4RH) n=175		Part-daily dose (2RHZE/4R3H3) n=175		Total n=350	
	n	%	n	%	n	%
Gender						
Male	73	41.7	103	58.9	176	50.3
Female	102	58.3	72	41.1	174	49.7
Ages (years)						
18-34	112	64.0	109	62.3	221	63.1
35-54	44	25.2	48	27.4	92	26.3
≥ 55	19	10.9	18	10.3	37	10.6
Duration of cough after ATD						
Data not available	46	26.3	10	5.7	56	16.0
Data available:	129	73.7	165	94.3	294	84.0
≤ 8 weeks	85	65.9	93	56.4	178	60.5
> 8 weeks	44	34.1	72	43.6	116	39.5
Diagnosis						
Clinical PTB	119	68.0	67	38.3	186	53.1
Bacteriological PTB	56	32.0	108	61.7	164	46.9
Duration of treatment						
< 9 months	115	65.7	135	77.1	250	71.4
≥ 9 months	60	34.3	40	22.9	100	28.6
Weight gained						
Data not available	2	1.1	5	2.9	7	2.0
Data available:	173	98.9	170	97.1	343	98.0
Yes	145	83.8	150	88.2	295	86.0
No	28	16.2	20	11.8	48	14.0

Table 2. Treatment Outcomes between Daily Dose and Part-daily Dose.

Treatment outcomes	Daily dose (2RHZE/4RH) n=175#		Part-daily dose (2RHZE/4R3H3) n=175		Total n=350		P value	PR (95% CI)
	n	%	n	%	n	%		
Success	156	89.1	160	91.4	316	90.3	0.470*	1.026 (0.957-1.099)
- Cured	23	13.1	69	39.4	92	26.3	< 0.001*	3.000 (1.966-4.579)
- Completed	133	76.0	91	52.0	225	64.0	< 0.001*	0.684 (0.580-0.807
Loss to follow up	18	10.3	14	8.0	32	9.1	0.458*	0.778 (0.399-1.514)
Failure	1	0.6	0	0.0	1	0.3	1.000**	-
Died	0	0.0	1	0.6	1	0.3	1.000**	-

CI, confidence interval; * chi-square test; ** exact Fisher test.; # reference group

Table 3. Adverse Effects in Continuation Phase between Daily Dose and Part-daily Dose.

Adverse effects	Daily dose (2RHZE/4RH) n=175#		Part-daily dose (2RHZE/4R3H3) n=175		Total n=350		P value	PR (95% CI)
	n	%	n	%	n	%		
Overall	18	10.3	24	13.7	42	12.0	0.324*	1.333 (0.751-2.367)
Gastrointestinal disorders (nausea, vomiting, heartburn)	5	2.9	12	6.9	17	4.9		
Skin disorders (pruritus, rash, acne)	2	1.1	2	1.1	4	1.1		
Musculoskeletal disorders (joint pain, myalgia)	2	1.1	2	1.1	4	1.1		
Neurological disorders (tingling, peripheral neuropathy)	1	0.6	3	1.7	4	1.1		
Hepatobiliary disorders (hiperbilirubinemia)	0	0.0	1	0.6	1	0.3		
Impaired kidney function	1	0.6	0	0.0	1	0.3		
Others (vertigo, hyperuricemia, general weekness)	4	2.3	6	3.4	10	2.9		

CI, confidence interval; * chi-square test; # reference group

found to be more in the part-daily dose group (13.7% vs. 10.3%, PR 1.333) but no significant difference (p = 0.324) was noted. The most common adverse effects in both groups were gastrointestinal disorders (4.9%). (**Table 3**)

PTB recurrence was experienced by three patients in the daily dose group and two patients in the part-daily dose group. The time of recurrence in both groups was >1 year after treatment completion. In the part-daily dose group, one patient had recurrence as lymphadenitis TB after four months of treatment completion.

DISCUSSION

In this study, the cure rates of both groups were lower than other studies in Asia and Africa, and the reported cure rates were 82.7% and 85.2%, respectively.[9,10] Suryanto, et al.[8] in South Sulawesi and Lienhardt, et al.[11] in 11 locations around Africa, Asia, and Latin America, reported cure rate of 92.4% and 93.9%, respectively. The low cure rates of both study groups were due to failure in conducting bacteriological examinations at the end of the intensive phase (two months) or at the end of treatment (≥ five months), especially in daily dose group, where

most patients already had no sputum at the end of the second month. Therefore, according to the WHO's and Indonesia's TB management guidelines, treatment outcome was defined as complete treatment. The definition of cure rates was not suitable for used because it requires sputum bacteriological examination for diagnosis and follow-ups, which was sometimes difficult to obtain at the beginning, second month, or the end of treatment.

Most bacteriological PTB patients had no cough within two months, especially in the daily dose group (70.8% vs. 46.4%). This condition limits the risk of disease transmission after two months of treatment.[12] This study showed that in term of lowering the risk of airborne transmission, daily dose is much better. This was consistent with the study conducted in Peru which showed that cough disappearance within two months after adequate treatment was 65%.[12] Other studies have shown that cessation of cough is related to the number of *mycobacteria* in the sputum and a successful culture conversion in sputum examination. This indicates that the presence or absence of cough represents the treatment response, especially in the first two months of treatment.[12]

The complete treatment rate was significantly higher in the daily dose group (76% vs 52%). It was because most patients in this group were diagnosed as clinically PTB (68% vs 38.3%). So, without the result of sputum examination before and after treatment, it can never be categorized as cured.

According to Indonesia's Health Profile (2017), the indicator used to evaluate TB treatment outcome was the "success rate," which is the sum of patients who were cured and underwent complete treatment. In this study, the success rates of the part-daily (91.4%) and daily dose regimens (89.1%) were equal to Indonesia's target (90%).[2] The success rates using the daily dose was similar to a meta-analysis by Kasozi et al.,[4] using the same regimen (90%). Weight gain was one of the important indicators for treatment success and in this study weight gain was also comparable between both study groups. These indicated comparable effectiveness between both groups.

The high cure and success rates of the part-daily dose in this study were supported by an in vitro study.[13] ATD in single or combination drugs could suppress *mycobacteria* growth for a certain period because it has post-antibiotic effects (PAE). Rifampicin is the most important ATD for TB treatment today because it can kill *mycobacteria* in the growth phase as well as the non-replicating phase. Besides, it has the longest PAE of approximately 67.8 hours (2.8 days), while isoniazid has only 18.1 hours (< 1 day). However, the combination of rifampicin and isoniazid has very long PAE approximately 159.8 hours (one week).[13,14] It means that part-daily dose is effective in suppressing *mycobacterial* growth. Gumbo et al.[14] revealed that a higher dose of rifampicin would suppress *mycobacteria* growth for much longer because it is a concentration-dependent antibiotic, and the PAE increases linearly with the Cmax/MIC ratio. Therefore, the duration of rifampicin concentration persists above the MIC (T > MIC), and the half-life is not as important. However, it is essential to optimize the PAE of rifampicin and prevent resistance because of its high Cmax/MIC ratio.[15] Rifampicin also reaches a steady-state intracellular concentration in 15 minutes, depending on the given dose; thus, it could immediately kill *mycobacteria* better than other ATDs.[14] Isoniazid is used because of its effectiveness, low price and rare adverse effects. However, it should not be administered as a single drug because it may cause resistance and recurrence.[16] Isoniazid is used to kill growing *mycobacteria* and depends on the AUC_{0-24}/MIC ratio.[15] Therefore, its ability to kill *mycobacteria* is mainly influenced by the duration of drug exposure above MIC (T > MIC) and drug concentration above MIC (C > MIC).

The failure rate in this study was similar to a meta-analysis of the RCTs in 2017, where both regimens did not significantly differ.[6] The patient who underwent treatment failure in this study was because of multidrug-resistant TB.

Since the success rate is similar between the two regimens, it is better to use the part-daily dose for the mass treatment of TB, because the possibility of poor compliance may be lower, although compliance was not measured in this

study.

Adverse Effects and Recurrence

In the continuation phase, there was no significant difference in the incidence of adverse effects between the groups, and no patient required treatment cessation. The most common side effect in both groups was gastrointestinal disorders (**Table 3**). This was in agreement with reports from Egypt, India, Pakistan, Philippine and Thailand for a daily dose, and South Sulawesi for a part-daily dose.[9,17] The recurrence event in this study was consistent with a meta-analysis of the RCTs (2017)—no significant difference was found between the daily or part-daily doses.[6]

CONCLUSION

The success rates of the daily or part-daily doses were equal to Indonesia's target for TB treatment (90%). The cure rate in the part-daily dose was better than the daily dose since more patients were confirmed bacteriologically. There were no significant differences in success, failure, loss to follow-up and death rates as well as adverse effects events in the continuation phase between the daily or part-daily doses.

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