Comparative Effectiveness of Tuberculosis Treatment Daily versus Intermittent Regimen in Indonesian TB-DM Patients: Real World Patient Database Study

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ABSTRAK

Latar belakang: *diabetes melitus (DM) meningkatkan risiko terjadinya TB aktif sebesar tiga kali; saat ini belum ada strategi pengobatan yang spesifik untuk pasien tuberkulosis-DM (TB-DM). Panduan WHO 2017 tidak lagi merekomendasikan pemberian obat secara intermiten pada pengobatan TB fase lanjutan karena tingginya risiko kegagalan, relaps, dan resistensi obat dibandingkan dengan pemberian setiap hari. Penelitian ini bertujuan untuk membandingkan efektivitas pengobatan fase lanjutan dengan kedua cara pemberian tersebut, dalam hal respons klinik dan konversi sputum, pada pasien TB-DM.* ***Metode:*** *studi kohort retrospektif menggunakan rekam medik pasien rawat jalan Rumah Sakit Pesahabatan, Jakarta mulai 1 januari 2015 hingga 31 desember 2018. Kriteria inklusi adalah semua pasien TB-DM berusia >18 tahun tanpa HIV dengan pemeriksaan sputum positif pada saat diagnosis, yang mendapat pengobatan kategori 1 dan telah memasuki fase lanjutan.* ***Hasil:*** *sebanyak 72 pasien memenuhi kriteri inklusi (75% laki-laki and 88.8% setidaknya memiliki hasil pemeriksaan sputum 1+ pada saat diagnosis). Tiga puluh subyek belum mengalami konversi pada awal pengobatan fase lanjutan. Pada akhir fase lanjutan, 44.2% pada kelompok intermiten dan 41.4% pada kelompok pengobatan setiap hari dinyatakan sembuh. Tujuh subyek mengalami efek samping; tetapi terdapat banyak pasien putus obat dan tidak dapat dijelaskan penyebab putus obat terkait dengan efek samping atau tidak.* ***Kesimpulan:*** *tidak didapatkan perbedaan dalam profil konversi sputum dan keberhasilan pengobatan TB kategori 1-DM fase lanjutan antara pemberian intermiten dan setiap hari pada pasien diabetes.*

Kata kunci: *TB-DM, diabetes melitus, fase lanjutan, pengobatan intermiten, pengobatan setiap hari, keberhasilan pengobatan.*

ABSTRACT

Background: *diabetes mellitus (DM) increases the risk of active TB by three times; there is no specific treatment strategy for tuberculosis-DM (TB-DM) patients. The 2017 WHO guidelines no longer recommended an intermittent regimen in the advanced phase of TB treatment due to higher risk of failure, relapse, and drug resistance compared to the daily regimen. This study aims to compare the effectiveness of treatment, in terms of clinical response and sputum conversion, of TB-DM patients in the advanced phase between the two-treatment delivery schedules.* ***Methods:*** *a retrospective cohort study from the medical records of patients from 1 January 2015 to 31 December 2018 at Persahabatan Hospital, Jakarta. The inclusion criteria are TB-DM patients aged >18 years with non-reactive HIV test, who have entered the advanced phase of category 1 TB treatment with smear positive at the time of diagnosis.* ***Results:*** *a total of 72 patients met the inclusion criteria. (75% male and 88.8%*

had at least 1+ smear results at the time of diagnosis). Thirty subjects still have positive smear at the beginning of the advance phase of treatment. After the advanced phase, 44.2% in the intermittent and 41.4% in the daily group were cured or having sputum conversion. Seven subjects had side effects; but there were lots of dropouts and it is unclear whether they dropped because of side effects or not. ***Conclusion:*** *there is no difference between sputum conversion profile and treatment success in advanced phase TB-DM treatment category 1 between the daily and intermittent regimen.ly for diabetic patients.*

Keywords: *TB-DM, diabetes mellitus, advanced phase, intermittent treatment, daily treatment, treatment success.*

INTRODUCTION

Tuberculosis (TB) is the largest cause of morbidity and mortality among infectious diseases in the world.[1] In 2017, 10 million people worldwide suffered from TB and 1.7 million people are estimated to have latent TB infection and at risk of developing active TB disease during their lifetime. Indonesia has the third highest number of TB cases in the world.[2] Early diagnosis and adequate therapy of TB patients are the primary treatment strategies.[3]

Diabetes mellitus (DM) increases the risk of active TB by three times,[4] and pulmonary TB is the 9th most frequent complication in DM.[5] The prevalence of TB-DM in Southeast Asia is 14% and 14.8% in Indonesia.[6] A systematic review revealed that TB prevalence in DM patients is around 1.7–36% and DM prevalence in TB patients is around 1.9–35%.[7] Patients with HbA1c ≥7% have 2.5 times greater risk of developing TB compared to those with HbA1c ≤7%.[8] Good glycemic control can reduce the risk of developing TB in DM patients.[9] The risk of death, treatment failure, and relapse is very high in TB-DM patients.[10,11] The risk of death is around 6.5–6.7 times higher in TB-DM patients.[12] Blood glucose management of DM patients in chronic inflammatory state is extremely difficult, while TB is a chronic inflammatory disease.[13] Recent research found that TB worsens glycemic control in DM patients, and failure of TB treatment in DM patients increases by 69% and risk of relapse four times.[14]

An optimal treatment strategy for TB-DM patients has not been found, and there is no scientific evidence supporting the difference in regimens between TB only and TB-DM patients.[13] Based on 2011 WHO guidelines, TB-DM management is the same as non-DM. In the intensive phase, four antituberculosis drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) are given daily for two months, followed by an advanced phase, in which two antituberculosis drugs (rifampicin and isoniazid) are given daily or intermittently three times a week for four months when blood sugar is well controlled, or it will be extended to seven months when blood sugar is poorly controlled.[15]

In 2017, World Health Organization (WHO) no longer recommended intermittent treatment in advanced phase. This was supported by a systematic review of intermittent therapeutic regimens in 2009; randomized control trials show that intermittent treatment has a higher risk of failure, relapse, and drug resistance compared to daily treatment.[16]

TB is diagnosed based on sputum examination,[3] which is also used for assessing treatment success. Sputum examination is usually performed at the end of the 2nd, 4th, and 5th month. The treatment of TB patient is considered unsuccessful if the sputum conversion is not achieved by the end of the fifth month of therapy.[17] No study in Indonesia has been conducted to compare the outcome of advanced phase treatment in TB-DM patients between intermittent and daily regimens. This study aims to compare the effectiveness of treatment in terms of clinical response and sputum conversion of TB-DM patients in the advanced phase between the two-treatment delivery schedules.

METHODS

This cohort retrospective study was conducted at Persahabatan Hospital, Jakarta. Data was taken

from all the medical records of TB-DM patients receiving category 1 TB treatment in the period of 1 January 2015 to 31 December 2018. The study secured ethical approval from the research ethics committee of Persahabatan Hospital. The inclusion criteria were TB-DM patients aged >18 years who had entered the advanced phase of TB treatment category 1 (2RHZE/4RH or 2RHZE/4R3H3) with smear positive at the beginning of TB treatment and non-reactive HIV test. The cohort were followed from the start of the adavanced phase up to the end of the treatment period. Data collected from the patients medical records, were analyzed comparing patients that had received the intermittent regimen using fixed dose combination (FDC) of three times a week and the ones that had received daily regimen using individual tablets. The dosage given was in accordance with the Indonesian guideline. This study observed the documented end results of treatment at the end of each patients advance phase. Statistical tests were performed using SPSS 20.0 and the method used to compare the results of treatment of the two groups (proportion of success) was X2 test.

This study has been approved by the Ethical Committee of Persahabatan Hospital (Reference number 25/KEPK-RSUPP/04/2019).

RESULTS

From 704 medical records of patient who registered as TB-DM patients from January 1, 2015 until December 31, 2018, 134 patients had entered the advanced phase of TB treatment category 1. From those 134 patients, only 72 patients met the inclusion criteria. **Table 1** presents the basic characteristics of these 72 patients. Fifty-four subjects (75%) were male, 68.1% were in the age group 46–65 , 76.4% had body weight 40–60 kg, and 64 patients had at least 1+ smear results (88.9%). Thirty patients (41.7%) did not reach conversion at the end of the intensive phase of treatment (**Table 2**). For seven

Table 1. Basic characteristics (N = 72)

	Intermittently thrice a week (N = 43) n (%)	Daily (N = 29) n (%)	Total n (%)
Sex			
- Male	31 (72.1)	23 (79.3)	54 (75.0)
- Female	12 (27.9)	6 (20.7)	18 (25.0)
Age group			
- 18–25 years	0	1 (3.4)	1 (1.4)
- 26–45 years	9 (20.9)	9 (31.0)	18 (25.0)
- 46–65 years	30 (69.8)	19 (65.5)	49 (68.1)
- >65 years	4 (9.3)	0	4 (5.6)
Body weight			
- <40 kg	1 (2.3)	1 (3.4)	2 (2.8)
- 40–60 kg	31 (72.1)	24 (82.8)	55 (76.4)
- >60 kg	11 (25.6)	4 (13.8)	15 (20.8)
Smear			
- 1–9 bar	5 (11.6)	3 (10.3)	8 (11.1)
- 1 positive	13 (30.2)	11 (37.9)	24 (33.3)
- 2 positive	12 (28.0)	6 (20.7)	18 (25.0)
- 3 positive	13 (30.2)	9 (31.0)	22 (30.6)

Table 2. Sputum conversion at the beginning of advance phase (N = 72)

Sputum conversion	Intermittently thrice a week (N = 43) - n (%)	Daily (N = 29) n (%)	Total n (%)	P value
Conversion	26 (60.5)	16 (55.2)	42 (58.3)	0.276
No conversion	17 (39.5)	13 (44.8)	30 (41.7)	

Table 3. Treatment result (N = 72)

Treatment result	Intermittently thrice a week (N = 43) - n (%)	Daily (N = 29) n (%)	Total n (%)	P value
Cure	19 (44.2)	12 (41.4)	31 (43.1)	0.634
Lost to follow up	23 (53.5)	15 (51.7)	38 (51.7)	
Failed	1 (2.3)	2 (6.9)	3 (4.2)	

Table 4. Adverse effect (N = 72)

Adverse effect	Intermittently thrice a week (N = 43) - n (%)	Daily (N = 29) n (%)	Total n (%)	P value
No	37 (86.0)	28 (96.6)	65 (90.3)	0.219
Itching	1 (2.3)	0	1 (1.4)	
Tingling	3 (7)	0	3 (4.2)	
Joint paint	2 (4.7)	0	2 (2.8)	
Nausea	0	1 (3.4)	1 (1.4)	

patients, conversion happened at the end of the 3rd month, and 12 patients dropped out before conversion. After the advanced phase, thirty-one subjects were cured (**Table 3**), 19 (44.2%) in the intermittent group and 12 (41.4%) in the daily group. Lost to follow up were similar for both groups (46.5% vs. 51.7%). Seven subjects had side effects (**Table 4**), 6 in the intermittent (14%) and 1 in the daily treatment (4%); but there were a lot of dropouts without information and it remained unclear whether they dropped out because of side effects or not.

DISCUSSION

In this study, the number of male subjects in both groups was greater than female subjects (75% vs 25%). This result is consistent with WHO's 2018 global report data which states that in 2017, the majority of TB patients were male,[2] and the 2017 International Diabetes Federation, which reported that DM mostly occurs in males.[18] The largest number of subjects were aged 46–65 years (68.1%) with body weight between 40–60 kg (76.4%), sputum examination results at least 1+ (88.8%), and 30 patients (41.7%) remain positive at the end of the intensive phase. The results is consistent with Riza et al.[13] who found that patients with TB-DM were mostly elderly, with a higher body mass index, and positive examination results, which usually remained positive at the end of the 2nd month of the intensive phase treatment.[13] Conversely, Har Ashish Jinda et al.[19] found that 32.7% remained positive at the end of the 4th week.

Success rate, failure, and dropouts were comparable in both groups. This differs from WHO's statement that the intermittent thrice a week regimen entails a higher risk of failure compared to the daily regimen.[16] Success rate in the intermittent group was only 44.2%, which differs from the treatment success observed in Mexico, 71.35%;[11] and treatment success in the daily group was only 41.4%, which differs from Cameroon's 90%.[20] Failure of treatment occurred in three patients, one in the intermittent group and two in the daily group. One in the daily group failed due to reversion at the end of the 5th month, and the others failed due to delayed sputum conversion until the end of 5th month of treatment, and their sputum culture results showed monoresistance to INH. This is in contrast to Argita et al.'s[21] study: TB patients with isoniazid monoresistance have the same response to sputum conversion and treatment results as patients who are sensitive to all tuberculosis drugs. These results were in accordance with the Ministry of Health of the Republic of Indonesia's report: the results of TB treatment in DM patients had a greater number of failures due to delayed sputum conversion.[22] Thirty- eight subjects were dropouts, 12 of them dropouts since they entered

the advanced phase and their follow up could not be performed. These results were similar with Mi Feng Ling et al.'s, that TB-DM patients have higher dropouts rate.[23]

Seven patients experienced side effects, mostly in the intermittent group (six vs. one). This result is different from Pranab Kumar Mandal et al.'s which reported more side effects in the daily treatment group.[24]

Strengths and Limitations of the Study

The strength of this study is that this is the first study comparing real world data of Indonesian TB-DM patients, assessing effectiveness and side effects of category 1 TB treatment at advanced phase between intermittent, thrice a week, and daily regimens. The data in this study was taken from the patients' medical record, and the large number of lost to follow up patients make it impossible to get the picture of these patients response. There were not enough patients to meet the number of samples needed in this study, eventhough we have included all eligible TB-DM patients, with the consequence of lower power of the study.

CONCLUSION

Treatment effectiveness in terms of clinical response and sputum conversion between intermittent group (three times a week), and daily treatment group during advanced phase in TB-DM patients were comparable.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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