Original article

Demographic and clinical factors associated with change of drug regimen due to adverse drug reactions among new tuberculosis patients in the upper north and upper northeast of Thailand: A secondary data analysis from a routine regional TB reporting system

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Objective This study aimed to identify demographic and clinical factors associated with change of the anti-TB drug regimen due to adverse drug reactions (ADRs) among new tuberculosis (TB) patients in the upper north and upper northeast regions of Thailand.

Methods A cross-sectional study was conducted among new TB patients in the areas of Disease Prevention and Control region 10 (the upper north area) from 1 Oct 2008 to 30 Sep 2013 and region 6 (the upper northeast area) from 1 Oct 2012 to 30 Sep 2013. Demographic and clinical data and the status of changing drug regimen were extracted from the Tuberculosis Clinic Management (TBCM) database. Multivariate logistic regression was used to analyze the association between change of drug regimen and the determinants.

Results Records were analyzed of 26,444 and 5,982 new TB patients in the upper north and upper northeast areas of Thailand, respectively. The overall incidence of anti-TB drug regimen change due to ADRs was 2.01%. Multivariate analysis of the study population revealed factors significantly associated with this change, including old age, and being registered in the upper north area, female, human immunodeficiency virus (HIV) co-infected, an anti-retroviral drug user, separate anti-TB tablet user, and having co-morbidities with hypertension, chronic kidney disease, liver disease, and cancer.

Conclusions Liver disease was a factor commonly associated with change of drug regimen due to ADRs among new TB patients in the two regional areas. Further clinical trials are needed to discover effective interventions during treatment for the prevention of ADRs among new TB patients with liver disease. Other associated factors should be monitored properly, based on this data analysis of new TB patients in each area. **Chiang Mai Medical Journal 2015;54(3):109-19**.

keywords: Tuberculosis, change of drug regimen, adverse drug reactions, the upper north of Thailand, the upper northeast of Thailand

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Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis complex (MTBC), which is transmitted through the air from an active pulmonary TB patient to others[1]. TB is a global public health concern. In 2013, the World Health Organization (WHO) estimated that TB was the second leading killer from a single infectious agent[2]. Globally, there were 9 million new TB patients with 1.5 million TB related deaths in 2013[2]. In Thailand, TB was ranked as the leading cause of death from a single infectious organism in 2013[3]. In that same year, 80,000 TB patients were newly diagnosed and 8,100 TB patients died[2].

Of the TB patients registered in Thailand during 2013, almost all of them (93%) were newly registered[4]. Therefore, the increased success in the outcome of overall TB treatment need to primarily focus on newly TB registered patients. Adverse drug reactions (ADRs) during treatment are a cause of unsuccessful TB treatment, especially among new TB patients. In addition, any major ADRs among the patients often prompted clinicians to stop the treatment and change the anti-TB regimen. A prospective study in China, conducted by Shang *et al*, showed that patients who developed anti-TB drug-induced hepatitis were nine times more likely to have unsuccessful treatment outcome[5]. In Thailand, the standard treatment regimen for new TB patients follows the WHO recommendation that is composed of isoniazid, rifampicin, pyrazinamide and ethambutol for two months before isoniazid and rifampicin for four months[1]. The major ADRs that commonly lead to a changing regimen for the "new TB patient" are hepatitis, rash, and ethambutol-induced visual disturbance[1]. The frequency of ADR occurrence among patients receiving treatment can be ordered as hepatitis (13.9%), gastrointestinal upset (10%), rash (7.5%), joint pain (3.2%), and visual disturbance (1.7%)[6]. Major ADRs to the first line anti-TB drugs in newly registered TB patients can cause morbidity and mortality. ADRs also increase patient suffering and patients can incur considerable additional expense due to hospitalization and extended duration of treatment[7,8]. Alternative regimens require a longer duration of treatment and they are often less effective[9]. The adverse events also are considered as a major determinant of treatment termination[10]. The sequelae have unfavourable treatment outcome, which includes death, loss to follow-up and treatment failure. In the worst public health scenario, patients who relinquish their treatment also may develop drug-resistant chronic infectious illnesses and transmit a drug-resistance strain to others in their communities. By using the Tuberculosis Clinic Management (TBCM) reporting system for the upper north and upper northeast regions of Thailand, this study aimed to identify the demographic and clinical factors associated with the change of the anti-TB drug regimen due to ADRs. The result of this study indicated the population at risk and could action an input for clinical trials and the implementation of prevention programs in the future.

Methods

A cross-sectional study among new TB patients in the areas of Office of Disease Prevention and Control region 10 (DPC10) and region 6 (DPC6) was carried out by using secondary data analysis from a routine regional TB reporting system.

Data source

TBCM is an off-line TB reporting system that originated in Sankhampang Hospital, Chiang Mai, Thailand. It reported on 97.94% and 100% of all district/provincial government hospitals in 8 upper north provinces of the DPC10 area in 2008 and 2009, respectively. The DPC10 area includes Mae Hong Son, Chiang Mai, Lamphun, Lampang, Chiang Rai, Phayao, Phrae, and Nan provinces. The use of the program has been extended beyond the original region, especially in the DPC6 area. However, in 2013, TB reporting covered 58.27% of all district/provincial government hospitals in nine northeast provinces of the DPC6 area, which includes Kalasin, Khon Kaen, Buengkan, Mahasarakham, Roi-et, Loei, Nong Khai, Nongbualamphu and Udon Thani provinces. The TB co-ordinator in each hospital keyed the TB patient data into the reporting system and sent it chronologically to the Provincial Health Office and Office of Disease Prevention and Control.

Data collection and management

By using the TBCM database, newly registered TB patients in DPC10 from 1 October 2008 to 30 September 2013 (5 fiscal years) and DPC6 from 1 October 2012 to 30 September 2013 (1 fiscal year) were identified and enrolled in this study. There were 26,836 and 6,119 patient records in DPC10 and DPC6, respectively. The duplication of patient records was managed by the responsible officers. The national identification number, first name, surname and date of birth were used for checking duplication of the patients. In the case of duplication among new TB patients, the earliest registered date of the individual was used for selection from the data. After the management of duplicated records, 26,444 and 5,982 patients' records in DPC10 and DPC6, respectively were included in the analytical part. Change of anti-TB drug regimen due to ADRs among new TB patients in both study areas was identified and based on data keyed into the TBCM database. Demographic (age and sex) and clinical data (e.g. human immunodeficiency virus (HIV) co-infection, anti-retro viral drug use, extra-pulmonary TB, separate anti-TB tablet use, co-morbidities with chronic diseases) were extracted from the database. Every patient record was de-identified before analysis. The year of ages in records that showed either minus value or 3 digits was identified as a missing value. These outliers accounted for 0.03% and 0.29% in records for DPC6 and DPC10, respectively. Permission to collect all the data had been granted by the directors of DPC10 and DPC6.

Definition and terms of dependent and independent variables

As a secondary data analysis in this study, the value of the dependent variables (change of anti-TB drug regimen due to ADRs) and independent variables (demographic and clinical determinants) relied on data keyed in by a trained TB co-ordinator in each hospital. For example, only one reason why a doctor prescribes a change of drug regimen need to be filled as a standard code number in the TBCM program. The TB co-ordinator selected a change of anti-TB drug regimen due to ADRs, and not because of drug resistance or other reasons, and this was defined as a positive value of the dependent variable. There was no detail about the clinical presentation of ADRs in this program. The annual TB training program for TB co-ordinators followed the latest guideline of the National Tuberculosis Programme, Thailand[1].

Data analysis

Baseline demographic and clinical factors described and compared the differences between patients in DPC10 and DPC6 by descriptive statistics (central tendency and proportion) and classical tests of hypothesis (two sample t-test for continuous data and two sample test of proportion for categorical data). The occurrence of changing anti-TB drug regimen due to ADRs was based on TBCM records and identified as binary outcomes (yes/no). There were some interesting demographic and clinical factors from the TBCM database that were identified hypothetically as independent variables. They were age group (0-14 years old, 15-59 years old and 59-99 years old), gender (male/female), HIV status (positive/negative), taking anti-retroviral drugs (yes/no), diagnosed with extra-pulmonary TB (yes/no), taking separate anti-TB tablets (yes/no), and having co-morbidities with chronic diseases such as diabetes (yes/no), hypertension (yes/no), chronic obstructive pulmonary disease (COPD) (yes/no), chronic kidney disease (yes/no), liver disease (yes/no) and cancer (yes/no). The demographic and clinical factors of patients prescribed and not prescribed to change the anti-TB drug regimen also were presented via descriptive statistics (proportion). The multivariate analysis for measurement of association between changing anti-TB drug regimen and demographic and clinical factors was analyzed by logistic regression. The backward elimination method, which had a P value cut-off point at 0.2 for variable removal from the model, also was applied for variable selection in the appropriate model. The diagram of data management and analysis is summarized and illustrated in Figure 1.

Results

After data cleaning, the 26,444 and 5,982 new TB patients in DPC10 and DPC6 were registered from 1 October 2008 to 30 September 2013 (5 fiscal years) and between 1 October 2012 and 30 September 2013 (1 fiscal year), respectively. Six hundred and fifty three new TB patients in the two regional areas were prescribed to change their anti-TB drug regimen due to ADRs, with an overall incidence of this change being 2.01%. According to the data, a small number of records were missing or unknown in some demographic and clinical characteristics, of which the number of records was therefore not equal to that of all inclusion data. Most of the demographic and clinical characteristics between samples in both regional areas were significantly different (Table 1).

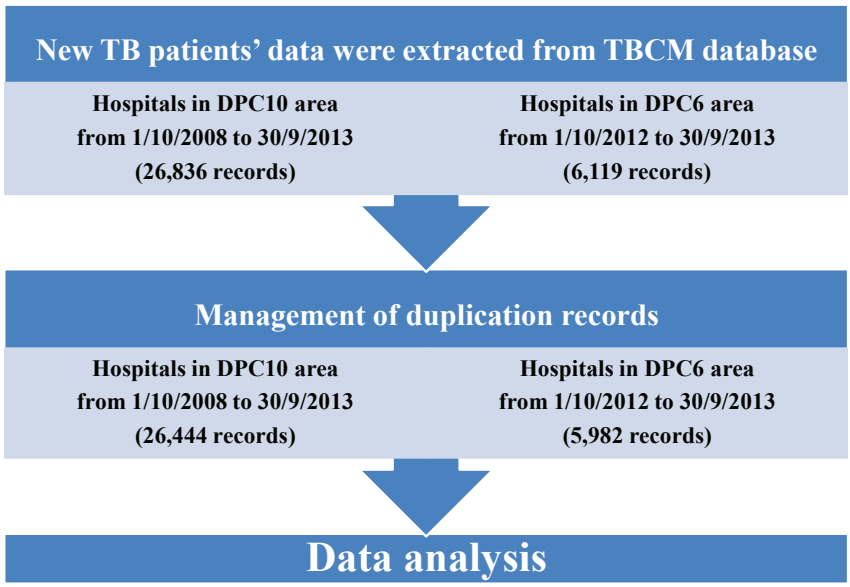

Figure 1. Diagram of data management and analysis in the study

Table 1. Demographic and clinical factors of the new TB patients in DPC10 and DPC6

Characteristics	DPC10	Observation Numbers	DPC6	Observation Numbers	*p* value
1.Demographic data					
Age (years)					
0-14	1.25%	26,367	0.87%	5,976	0.01**
15-59	64.57%	26,367	60.37%	5,976	< 0.01**
60-99	34.18%	26,367	38.76%	5,976	< 0.01**
Total of all ages	100%	26,367	100%	5,976	< 0.01*
Mean of all ages (SD)	51.71 (18.26)	26,367	52.96 (17.15)	5,976	0.01**
Female	30.80%	26,438	32.50 %	5,963	
2. Clinical information					
Changing drug regimen due to ADRs	2.27%	26,444	0.89%	5,982	< 0.01**
HIV co-infection	17.83%	23,656	9.31%	4,758	< 0.01**
Anti-retroviral drug use	9.63%	25,721	5.06%	5,571	< 0.01**
Extra-pulmonary TB	18.22%	26,440	15.75%	5,981	< 0.01**
separate anti-TB tablet use	74.35%	26,444	69.09%	5,982	< 0.01**
Diabetes	4.23%	26,444	11.18%	5,982	< 0.01**
Hypertension	5.47%	26,444	5.30%	5,982	0.59**
Chronic kidney disease	0.70%	26,444	1.17%	5,982	< 0.01**
Liver disease	0.34%	26,444	0.27%	5,982	0.40**
COPD	2.80%	26,444	1.67%	5,982	< 0.01**
Cancer	0.14%	26,444	0.35%	5,982	< 0.01**

*Analyzed by the two sample t test of unequal variance, ** Analyzed by the two sample test of proportion

The elderly age group was the most likely to change their anti-TB regimen due to ADRs, as they were in the highest proportion of patients. The percentage of female patients changing their anti-TB regimen was higher than that for men. TB patients who presented with a positive value of clinical variables showed higher percentages of changing anti-TB regimen due

to ADRs, when compared to those who did not. The demographic and clinical determinants of TB patients who were and were not prescribed for changing their anti-TB drug regimen due to ADRs are illustrated in Table 2.

The multivariate analysis of all variable models (full model) revealed that factors significantly associated with changing anti-TB drug regimen due to ADRs among new TB patients were of the elderly age group (OR=1.53, 95% CI=1.26–1.85), registered in DPC10 (OR= 2.24, 95%CI=1.67–3.01), female (OR=1.25, 95% CI=1.05–1.48), HIV co-infected (OR=1.61, 95% CI=1.18–2.19), using anti-retroviral drugs (OR= 1.85, 95%CI=1.32–2.58), using separate anti-TB tablets (OR=1.37, 95%CI=1.12–1.66), and having co-morbidities with hypertension (OR= 1.43, 95%CI= 1.04–1.97), chronic kidney disease (OR=2.56, 95%CI= 1.43–4.56), liver disease (OR=7.15, 95%CI= 3.74–13.67), and cancer (OR=3.81, 95%CI= 1.35–10.78), as shown in Table 3. The area under the receiver operating characteristics (ROC) curve of the logistic model for change of anti-TB drug regimen between all variables (full model), and significantly associated variables (reduced model), were the same at two decimal points (0.66).

The result of backward elimination showed that the appropriate model was the same as the significantly associated variable model (reduced model), which did not include extra-pulmonary TB, diabetes or COPD variables.

In the case of subgroup analysis by regional area, the multivariate analysis of DPC10 data in all variable models (full model) revealed that changing anti-TB drug regimen due to ADRs among newly registered TB patients was as-

Table 2. Demographic and clinical factors of changing and not changing the anti-TB drug regimen due to ADRs among newly registered TB patients in two regional areas

Characteristics	Number of anti-TB drug regimens due to ADRs changed	Number of anti-TB drug regimens due to ADRs not changed
Age groups (row %)		
0-14 years old	2 (0.52)	381 (99.48)
15-59 years old	391 (1.90)	20,241 (98.10)
60-99 years old	258 (2.28)	11,070 (97.72)
Gender (row %)	Female: 238 (2.36)	Female: 9,848 (97.64)
	Male: 415 (1.86)	Male: 21,900 (98.14)
HIV status (row %)	Positive: 171 (3.67)	Positive: 4,490 (96.33)
	Negative: 450 (1.89)	Negative: 23,303 (98.11)
Anti-retro viral drug use (row %)	Yes: 123 (4.46)	Yes: 2,636 (95.54)
	No: 518 (1.82)	No: 28,015 (98.18)
Extra-pulmonary TB (row %)	Yes:132 (2.29)	Yes: 5,627 (97.71)
	No: 521 (1.95)	No: 26,141 (98.05)
Separate anti-TB tablet use(row %)	Yes:517 (2.17)	Yes: 23,278 (97.83)
	No: 136 (1.58)	No: 8,495 (98.42)
Diabetes (row %)	Yes: 42 (2.35)	Yes: 1,746 (97.65)
	No: 611 (1.99)	No: 30,027 (98.01)
Hypertension (row %)	Yes: 57 (3.23)	Yes: 1,707 (96.77)
	No: 596 (1.94)	No: 30,066 (98.06)
Chronic kidney disease (row %)	Yes: 14 (5.49)	Yes: 241 (94.51)
	No: 639 (1.99)	No: 31,532 (98.01)
Liver disease (row %)	Yes: 14 (13.33)	Yes: 91 (86.67)
	No: 639 (1.98)	No: 31,682 (98.02)
COPD (row %)	Yes: 22 (2.63)	Yes: 816 (97.37)
	No: 631 (2.00)	No: 30,957 (98.00)
Cancer (row %)	Yes: 4 (6.78)	Yes: 55 (93.22)
	No: 649 (2.01)	No: 31,718 (97.99)

Table 3. Multivariate analysis of factors associated with changing the anti-TB drug regimen due to ADRs among newly registered TB patients in two regional areas

Factors	All variable models (full model) n=27,969		Significant variable selected model (reduced model)** n=27,974	
	Adjusted OR	95%CI (*p* value)	Adjusted OR	95%CI (*p* value)
Age groups				
0-14 years old	0.38	0.09 - 1.55 (0.18)	0.38	0.09–1.53 (0.17)
15-59 years old (reference group)	-	-	-	-
60-99 years old	1.53	1.26 - 1.85* (< 0.01)	1.52	1.26-1.83* (< 0.01)
Registered in DPC10	2.24	1.67 - 3.01* (< 0.01)	2.19	1.64-2.94* (< 0.01)
Female	1.25	1.05 - 1.48* (0.01)	1.25	1.06-1.48* (< 0.01)
HIV co-infection	1.61	1.18 - 2.19* (< 0.01)	1.59	1.17-2.16* (< 0.01)
Antiretroviral drug use	1.85	1.32 - 2.58* (< 0.01)	1.85	1.32-2.58* (< 0.01)
Extra-pulmonary TB	0.99	0.80 - 1.22 (0.92)	Excluded	
Separate anti-TB drug use	1.37	1.12 - 1.66* (< 0.01)	1.36	1.12-1.66* (< 0.01)
Diabetes	1.24	0.87-1.77 (0.23)	Excluded	
Hypertension	1.43	1.04 - 1.97* (0.03)	1.51	1.11-2.05* (< 0.01)
Chronic kidney disease	2.56	1.43 - 4.56* (< 0.01)	2.62	1.47-4.66* (< 0.01)
Liver disease	7.15	3.74 - 13.67* (< 0.01)	7.20	3.77-13.77* (< 0.01)
COPD	0.95	0.58 – 1.56 (0.85)	Excluded	
Cancer	3.81	1.35 - 10.78* (0.01)	3.83	1.36-10.80* (0.01)

*Statistically significant at *p* value < 0.05,

** No extra-pulmonary TB, diabetes or COPD variables in the reduced logistic model

sociated with the elderly age group (OR=1.58, 95%CI= 1.30–1.93), being female (OR=1.24, 95%CI=1.04–1.48), HIV co-infection (OR= 1.67, 95%CI=1.21–2.29), anti-retroviral drug use (OR= 1.76, 95%CI=1.25–2.48), separate anti-TB tablet use (OR=1.39, 95%CI=1.13–1.72), co-morbidities of hypertension (OR= 1.58, 95%CI=1.14–2.19) and liver disease (OR=4.77, 95%CI= 2.16–10.55), as shown in Table 4. The multivariate analysis of DPC6 data in all variable models (full model) revealed that changing anti-TB drug regimen due to ADRs was associated with co-morbidities of liver disease (OR= 43.61, 95%CI=12.87–147.77), chronic kidney disease (OR=18.03, 95%CI= 5.71–56.96) and cancer (OR=14.69, 95%CI= 3.18–67.83), as also shown in Table 4. If the significant variable of the selected model (reduced model), which did not include extra-pulmonary TB, diabetes or COPD, was used to predict the change of anti-TB drug regimen due to ADRs, the area under the ROC curve that reflects the accuracy of outcome prediction would be 0.63 and 0.69 in DPC10 and DPC6, respectively.

Discussion

According to multivariate analysis in the two regional areas (DPC10 and DPC6), results showed that being elderly (60 years or older), registered in DPC10, female, HIV co-infected, an antiretroviral drug user, and separate anti-TB tablet user, with co-morbidities such as hypertension, chronic kidney disease, liver disease and cancer was associated significantly with change of anti-TB drug regimen due to ADRs. Any serious ADRs among the patients have influenced doctors to stop treatment and change the anti-TB regimen. There were a number of cohort studies that supported the association between the elderly (60 years or older) and any major ADRs among patients receiving first-line anti–TB drugs. The elderly were associated significantly with major ADRs by 2 times (95% CI, 1.5-2.8) in a study by Marra *et al*[6] and 3 times

Table 4. Multivariate analysis of factors associated with changing the anti-TB drug regimen due to ADRs among newly registered TB patients by regional area

Associated factors	DPC10 (n=23,301)		DCP6 (n=4,633)	
	Adjusted OR	95%CI (*p* value)	Adjusted OR	95%CI (*p* value)
Age groups				
0-14 years old	0.41	0.10-1.66 (0.21)	No event occur	No event occur
15-59 years old (reference group)	-	-	-	-
60-99 years old	1.58	1.30-1.93* (< 0.01)	1.08	0.57-2.05 (0.81)
Female	1.24	1.04-1.48* (0.02)	1.30	0.71-2.38 (0.39)
HIV Co-infection	1.67	1.21-2.29* (< 0.01)	0.80	0.13-4.74 (0.80)
Antiretroviral drug use	1.76	1.25-2.48* (< 0.01)	4.89	0.76-31.57 (0.10)
Extra-pulmonary TB	1.02	0.82-1.26 (0.87)	0.65	0.27-1.59 (0.35)
Separate anti-TB drug use	1.39	1.13-1.72* (< 0.01)	1.13	0.58-2.19 (0.71)
Diabetes	1.34	0.92-1.95 (0.13)	0.74	0.27-2.03 (0.55)
Hypertension	1.58	1.14-2.19* (0.01)	0.36	0.07-1.73 (0.20)
chronic kidney disease	1.76	0.87-3.56 (0.12)	18.03	5.71-56.96*(< 0.01)
liver disease	4.77	2.16-10.55* (< 0.01)	43.61	12.87-147.77*(< 0.01)
COPD	0.90	0.53-1.50 (0.68)	1.34	0.27-6.54 (0.72)
Cancer	2.19	0.52- 9.30 (0.29)	14.69	3.18-67.83* (< 0.01)

*Statistically significant at *p* value < 0.05

(95% CI, 1.3-6.3) by Yee *et al*[9]. According to a review article, the reviewers recommend that liver injury, due to first-line anti-TB drugs, should be given special attention in patients over 60 years old[11]. Female patients also were included in the risk population, according to evidence in studies from Marra et al and Yee *et al*. Their work showed that the female sex had a higher chance of developing major ADRs by 1.6 times (95%CI, 1.3–2.0) and 2.5 times (95%CI, 1.3 to 4.7) respectively[6,9]. In addition, the HIV positive population has increased risk of serious ADRs by almost 4 times (95% CI, 1.05 to 13.4)[9]. Anti-retroviral drugs and first-line anti-TB drugs have similar side effects, for example, severe rash, gastrointestinal upsets and hepatitis[1,12]. Therefore, taking both anti-TB and anti-retroviral drugs gives a high chance of developing ADRs, and may result in a change of anti-TB drug regimen. Rifampicin is a first line anti-TB drug known as a cytochrome p450 inducer. Therefore, it interacts with hundreds of drugs, including antiretroviral, anti-hypertensive, diuretic, anti-cancer, analgesic, immunosuppressant, hypnotic and anti-depressant drugs via a decrease in the level of the drugs in the blood[13]. Symptomatic illnesses, which are related to poor control of chronic diseases, are caused by drug interaction with rifampicin and may influence doctors to change the anti-TB drug regimen from a rifampicin-based regimen to something else. The amount of milligrams in isoniazid, rifampicin, pyrazinamide and ethambutol prescriptions is not equal between separate tablets and fixed dose combinations (FDCs) when related to each weight group[1]. Separate tablets normally have a higher dosage than FDCs for each weight level[1]. A study at a TB clinic in Khon Kaen supported the association between ADRs and separate anti-TB tablets among newly registered TB patients[14]. Comorbidity with liver disease and drug-induced hepatitis (a common ADR of first-line anti-TB drugs) is a simple association, which explains that a first-line anti-TB regimen almost always contains hepatotoxic drugs and therefore the drugs will deteriorate the condition of TB patients with poorly functioning liver. There is significant evidence to support this association[6,15,16].

Not surprisingly, co-morbidity with liver disease was one common factor significantly associated with changing anti-TB drug regimen due to ADRs in both DPC10 and DPC6. Symptom-related liver injury can be observed commonly in patients with pre-existing liver disease and who also received the first-line anti-TB regimen, of which almost all drugs are hepatotoxic. The other characteristic, which was quite close between both regional areas, formed the very rare occurrence of changing anti-TB drug regimen due to ADRs in a young age population (0-14 years old). There were none and only two children who experienced such an event in DPC6 and DPC10, respectively. This finding explains that young age increases anti-TB excretion, and therefore ADRs are very unusual in children[17].

The proportion of patients who were prescribed a change of anti-TB drug regimen due to ADRs in DPC10 (2.27%) was much higher than that in DPC6 (0.89%), which could be explained hypothetically by the proportion of significantly associated factors with major ADRs in previous studies[9,14]. For example, TB-HIV co-infection and prescribed separate anti-TB tablets were clearly higher in DPC10 when compared with those in DPC6.

The discordances of the significantly associated demographic and clinical determinants between DPC10 and DPC6 were being elderly, female, HIV positive, an anti-retroviral drug user, separate anti-TB tablet user, and having hypertension, chronic kidney disease and cancer. These disagreements between the two regional areas could be explained by observation of numbers, time period of subject recruitment, characteristics of demographic data and clinical factors being different, as shown in Table 1. TB reporting coverage among provincial and district hospitals (100% in DPC10 and 58.27% in DPC6) also might influence discordant results. The low reporting coverage in DPC6 may result in random error and selection bias in the study. The characteristics of demographic and clinical factors and changes of anti-TB regimen due to ADRs in DPC6 could be different between hospitals where some of them submit their report through the TBCM system and others do not. In addition, the proportion of liver and bile duct cancer among all cancers in DPC10 was much lower than that in DPC6 (2.91% versus 16.96%)[18]. Liver and biliary tract cancer damage normal liver function, and therefore hepatotoxic anti-TB drugs cannot be detoxified effectively.

As this study is a secondary data analysis, some bias could have occurred, similar to other studies that use the same kind of data; for example, information bias, selection bias, and confounding factors. The information bias could encompass doctor prescriptions, the value of variables given by TB co-coordinators, and some technical errors in the TBCM program during version upgrade. Each clinical judgment on changing the anti-TB regimen and the individual decision of TB co-coordinators to provide the value of variables in the TBCM program may differ. Selection bias could be found in DPC6, as it has low reporting coverage. Confounding factors that cause a change of anti-TB drug regimen due to ADRs, and also relate to significant factors in this study, could be unknown determinants. For example, the tolerance threshold of ADRs in patients may be associated with gender and age, and these factors consequently influence the doctor in changing the drug regimen. Co-administration of particular drugs for treating co-morbidities may be associated with the change of anti-TB drug regimen due to ADRs. These confounding factors could not be explored in this study. Although the occurrence of ADRs in this study was rare (2.01%), 653 people experienced ADR events. The sample size for these events was acceptable for analysis with the logistic regression model, according to suggestion by Paul Allison in his topic; “logistic regression for rare events”[19]. The results of this study can conclude that all significant factors were associated with the “change of anti-TB drug regimen due to any ADRs”, especially in DPC10, which had 100% reporting coverage and they are able to be generalized. Although the “changing anti-TB drug regimen due to ADRs” (dependent variable of this study) is a consequence of ADRs, the results cannot conclude directly that all significant factors were associated with ADRs.

As co-morbidity with liver disease was a common factor with a high degree of association, special attention and intervention were needed to prevent or de-escalate the change of anti-TB regimen due to ADRs during TB treatment. Further clinical trials may be needed to discover effective interventions. Other risk factors such as old age, HIV co-infection with or without antiretroviral drug use, separate anti TB tablet use, co-morbidity with chronic kidney disease (CKD), hypertension (HT) or cancer should be monitored properly, based on a high risk population identified in this studyin each area.

Limitations

As the results of this study were based on secondary reporting data (TBCM), a difference of individual clinical judgements and human error, while giving the value of variables in the reporting system, could have occurred. A number of important determinants were not prepared for collection in advance; for example, no details for changing the anti-TB regimen due to ADRs (hepatitis, rash, gastrointestinal upset), and no exact date of the anti-TB drug regimen change, with neither the completion day of drug re-challenge nor reporting day being prepared. Missing data of some characteristics could interfere with the results, especially missing records that contained positive value of the dependent variable.

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Conflict of Interest

All authors declared no conflicts of interest.

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ปัจจัยด้านประชากรและคลินิกที่สัมพันธ์กับการเปลี่ยนยารักษาวัณโรคที่มีสาเหตุจากการแพ้ยาในกลุ่มผู้ป่วยวัณโรครายใหม่ของเขตภาคเหนือตอนบนและภาคอีสานตอนบนของประเทศไทย: การศึกษาโดยใช้ข้อมูลทุติยภูมิจากระบบรายงานวัณโรคปกติระดับเขต

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วัตถุประสงค์ เพื่อศึกษาปัจจัยด้านประชากรและคลินิกที่สัมพันธ์กับการเปลี่ยนยารักษาวัณโรคที่มีสาเหตุจากการแพ้ยาในกลุ่มผู้ป่วยวัณโรครายใหม่ที่ขึ้นทะเบียนรักษาในเขตภาคเหนือตอนบนและภาคอีสานตอนบนของประเทศไทย

วิธีการศึกษา ดำเนินการศึกษาแบบตัดขวางเชิงวิเคราะห์ (cross-sectional study) ในกลุ่มผู้ป่วยวัณโรครายใหม่ ที่ขึ้นทะเบียนรักษาในพื้นที่รับผิดชอบของ สำนักงานป้องกันควบคุมโรคที่ 10 (ภาคเหนือตอนบน) ตั้งแต่วันที่ 1 ตุลาคม 2551 ถึง 30 กันยายน 2556 และสำนักงานป้องกันควบคุมโรคที่ 6 (ภาคอีสานตอนบน) ตั้งแต่วันที่ 1 ตุลาคม 2555 ถึง 30 กันยายน 2556 โดยเก็บข้อมูลด้านประชากร ด้านคลินิก และข้อมูลการเปลี่ยนยาวัณโรคที่มีสาเหตุจากการแพ้ยา จากฐานข้อมูลโปรแกรมบริหารงานคลินิกวัณโรคระดับเขตในพื้นที่ศึกษา ดำเนินการหาความสัมพันธ์ระหว่างปัจจัยด้านประชากรและคลินิกกับการเปลี่ยนยาวัณโรคที่มีสาเหตุจากการแพ้ยาโดยใช้การวิเคราะห์หาความสัมพันธ์แบบพหุตัวแปรด้วยการทดสอบแบบถดถอยโลจิสติก

ผลการศึกษา จากข้อมูลผู้ป่วยวัณโรครายใหม่จำนวน 26,444 ราย ในพื้นที่ภาคเหนือตอนบน และ 5,982 ราย ในพื้นที่ภาคอีสานตอนบน พบอุบัติการณ์ของการเปลี่ยนยาวัณโรคที่มีสาเหตุจากการแพ้ยาที่ร้อยละ 2.01 ผลการวิเคราะห์หาความสัมพันธ์แบบพหุตัวแปรในกลุ่มประชากรศึกษาทั้งหมดพบว่า ปัจจัยที่สัมพันธ์กับการเปลี่ยนยาที่มีสาเหตุจากการแพ้ยา ได้แก่ ผู้สูงอายุ ขึ้นทะเบียนรักษาในพื้นที่ภาคเหนือตอนบน เพศหญิง การติดเชื้อเอชไอวีร่วม การกินยาต้านไวรัสเอชไอวีร่วม การกินยาวัณโรคแบบแยกเม็ด ความดันโลหิตสูง โรคไตเรื้อรัง โรคตับ และโรคมะเร็ง

สรุปผลการศึกษา การมีโรคตับร่วมเป็นปัจจัยที่สัมพันธ์กับการเปลี่ยนยาวัณโรคที่พบได้ทั้งสองพื้นที่ ดังนั้นการศึกษาเชิงทดลองทางคลินิกในอนาคตเพื่อหาวิธีการป้องกันผลข้างเคียงจากยาในกลุ่มประชากรนี้ จึงเป็นสิ่งจำเป็นที่ต้องการการศึกษาต่อไป สำหรับผู้ป่วยวัณโรครายใหม่ที่มีปัจจัยสัมพันธ์อื่นๆร่วม มีความจำเป็นที่จะต้องเฝ้าระวังการแพ้ยาในระหว่างการรักษา ตามความเหมาะสมของแต่ละพื้นที่ **เชียงใหม่เวชสาร 2558;54 (3):109-19.**

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