Clinical Features and Outcomes of Isoniazid Mono-Resistant Pulmonary Tuberculosis

Nitipatana Chierakul MD*,
Vorachai Saengthongpinij MD*, Suporn Foongladda DVM, PhD**

** Division of Respiratory Disease and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Objective: *To determine the characteristics of pulmonary tuberculosis (TB) patients harbored organisms with isoniazid mono-resistant drug susceptibility pattern.*
Material and Method: *A retrospective review of medical records for all culture-proven adult pulmonary TB patients in Siriraj Hospital between July 2009 and July 2011 was conducted. Demographic data, clinical presentations, and radiological characteristics were recorded and compared between isoniazid mono-resistant and other-resistant groups. Treatment regimens with outcome determination of patients infected with isoniazid mono-resistant strains were also verified.*
Results: *Among 489 patients during the present study period, 28 were infected with isoniazid mono-resistant strain (5.7%). The mean age was 53±18 years, and 8% of them had a history of previous treatment in the past. When compared with those infected with any other form of resistant strains, isoniazid mono-resistant pulmonary TB patients tended to have less radiographic cavitary lesion (8.3% vs. 26.7%, p = 0.006) but no significant difference was seen in term of demographic data and clinical presentations. All of them who had completed the treatment were cured. No difference in cure rate and relapse rate among patients treated with quinolone or non-quinolone containing regimens.*
Conclusion: *Isoniazid mono-resistance shares common clinical features with other resistances pulmonary TB, except for less cavitary lesion from initial chest radiograph. Appropriate drug susceptibility testing with prompt regimen adjustment can lead to a favorable treatment outcome.*

Keywords: *Isoniazid mono-resistant, Pulmonary tuberculosis, Clinical feature, Treatment regimen, Treatment outcome*

J Med Assoc Thai 2014; 97 (Suppl. 3): S86-S90
Full text. e-Journal: *http://www.jmatonline.com*

Tuberculosis (TB) remains a major public health problem due to it burden both in term of prevalence and mortality. At present, World Health Organization has classified Thailand as one of the high TB burden countries[1]. Treatment option initially in the past was only with single agent namely streptomycin and an instant drug resistance was encountered. Development of other agents and different regimen clinical trials in the past decades led to current standard short course chemotherapy. Despite the availability of anti-tuberculosis drugs, drug-resistant tuberculosis (DR-TB) gradually emerges. Among drug-resistant TB isolates in the United States, isoniazid (INH) mono-resistance was one of the most commonly observed with the prevalence of 4.2% in 2005[2]. According to the Thailand National Survey in 2006-2007, INH resistance was encountered in 14.7% of sampling TB cases[3].

Although resistance to INH is not uncommon among *Mycobacterium tuberculosis* isolates, there have been few studies on the clinical characteristics and treatment outcomes of patients infected with INH mono-resistance. From a systematic review and meta-analysis published in 2009, conclusion could not be drawn for the efficacy of current standardized retreatment regimen in persons with INH mono-resistance[4]. A report from Korea that evaluated treatment outcomes of 36 patients with INH mono-resistant and 3 with combined INH and streptomycin resistant pulmonary TB, with 3 different regimens (2HRZE/10RE, 2HRZE/7RE, and 2HRZE/4RZE: H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; number, months of treatment). Successful treatment was established in 92% of the patients, with additional acquired resistance developed in two out of three failure patients, with rifampicin in 1 patient and

Correspondence to:
Chierakul N, Division of Respiratory Disease and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: 0-2419-7757, Fax: 0-2419-7758
E-mail: nitipat7@gmail.com

pyrazinamide in 1 patient. Radiographic cavitary and extensive parenchymal lesions were common in those with treatment failure[5].

Based on the current World Health Organization guidelines that recommend the use of rapid drug susceptibility testing (DST) for early detection of resistance to both rifampicin and INH (multidrug-resistant tuberculosis, MDR-TB) or rifampicin alone. The optimal regimen for the treatment in patients who harbored INH mono-resistant strains has not been determined, and benefits may be less if suboptimal regimens are used[6]. In the present study, we aim to characterize the clinical features of INH mono-resistant in comparison with other resistant *Mycobacterium tuberculosis* from patients with pulmonary tuberculosis in Thailand. The clinical outcomes after treatment in INH mono-resistant were also categorized.

Material and Method

A retrospective study was conducted by reviewing the medical records for all culture-proven adult pulmonary tuberculosis patients in Siriraj Hospital between July 2009 and July 2011. We included the patients whose age was more than 15 years, had DST results, and clinical information was completed. Demographic data, clinical presentations, radiological characteristics, and treatment regimens with outcome determination according to standardized criteria[6] were collected. Permission to conduct the study was approved by the Siriraj Institutional Review Board (Si 140/2012).

Subject characteristics were demonstrated using percentage and mean with standard deviation. INH mono-resistant was defined as isolates which resisted to only isoniazid at low level, any INH resistant TB except for MDR-TB as combined isoniazid and other drugs resistance except for rifampicin, and extensively drug-resistant TB as MDR-TB with additional aminoglycoside and quinolone resistances. Comparison between subjects with INH mono-resistant and other resistant TB groups was also determined according to the data characteristic, by using unpaired t-test or Chi-square test where appropriate. A two-tailed p-value <0.05 was considered as denoting statistical significance. The statistical software SPSS version 18.0 was employed for all the analyses performed.

Results

A final total of 486 culture-proven adult pulmonary tuberculosis patients who fulfilled our inclusion criteria were verified during the present study period, any drug-resistant TB were encountered in 116 patients (23.7%). The prevalence of INH mono-resistant was 5.7% (28/486). Any INH resistant TB except for MDR-TB, MDR-TB, and extensively drug-resistant TB were found in 11.5%, 4.9%, and 0.8% of the total patients, respectively.

The mean age of the INH mono-resistant group was 53 ± 18 years; 10 of them (35.7%) had positive sputum smears. When compared with patients infected with other resistant strains, they tended to have significant less cavitary lesion on an initial chest radiograph, but no significant difference was seen in term of age, gender, co-morbidities, clinical presentations, and sputum-smeared status (Table 1).

Treatment regimens and outcomes

Among 28 patients, only 20 of them had treatment outcome determination, the rest were transferred out and lost to follow-up. All of the patients initially received standard regimen of 2HRZE/4HR without directly observed therapy. After the DST results revealed INH mono-resistant *Mycobacterium tuberculosis* isolates, INH was discontinued and the regimen was adjusted according to the preference of physician in charge as listed in Table 2. However, there were 3 patients without regimen modification due to the late recognition of DST results.

An average follow-up period for those with outcome determination was 28 (19-35) months. After complete treatment with various regimens, all were cured. No difference in cure rate was found among patients treated with ofloxacin (10 patients) and non-ofloxacin containing regimens (10 patients). However, relapse occurred in one patient who received ofloxacin (O) (2RZEO/6REO) after finished the regimen for 11 months, but the DST at the time of relapse revealed a fully susceptible strain.

Discussion

Global confrontation with DR-TB is one of the major obstacles for TB control. Effective management of DR-TB requires prompt case detection, effective treatment regimens, active preventive measures, and systematic surveillance activities. A short time to drug-resistant diagnosis may increase the likelihood of starting appropriate treatment early, hence increase cure rates, decrease mortality, and also reduce the development of additional drug resistance. Resistance to INH alone, or in combination, is one of the most common phenotypes encountered locally in

Table 1. Demographic data of patients infected with resistant isolates

Parameter	INH mono-resistance (n = 28)	Other resistance (n = 88)	p-value
Age (mean ± SD, years)	53±18	47±20	0.14
Male sex (%)	40.7	52.9	0.27
Diabetes mellitus (%)	16.7	13.2	0.74
HIV co-infection (%)	4.2	11.8	0.44
Corticosteroid use (%)	8.3	3.9	0.59
Other immunosuppressive states (%)	8.3	2.6	0.24
Previously treated tuberculossi (%)	8.3	11.8	1.00
Active smoking (%)	20.8	31.1	0.33
Clinical presentations			
Cough (%)	75.0	72.4	0.80
Hemoptysis (%)	16.7	14.5	0.75
Fever (%)	12.5	27.6	0.13
Weight loss (%)	37.5	43.4	0.61
Dyspnea (%)	20.8	18.4	0.77
Radiographic cavitary lesion (%)	8.3	26.7	0.006*
Positive smear (%)	35.7	34.1	0.78

HIV = human immunodeficiency virus

Table 2. Treatment option in 20 patients infected with INH mono-resistant MTB

Regimen	Number
Ofloxacin containing	
6REO	2
6RZEO	2
1RZEO/6RZE	1
2RZEO/6REO	1
2RZES/4RZEO/2REO	1
2RZE/7REO	1
2REO/10RE	2
Non-ofloxacin containing	
2HRZE/4HR	3
6RZE	3
9RZE	3
2RZE/7RE	1

H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; O = ofloxacin; numeric number in front of regimen, months of treatment

Thailand and all over the world. Recently, an outbreak of INH mono-resistant TB among prisoners and recreational drug users was reported from London during 2000-2006[7].

The prevalence of isoniazid mono-resistance in the present study was comparable to those report from Israel and slightly higher than from the United States and some countries in Europe[2,8-11]. In comparison with susceptible TB cases, treatment of active or latent TB in the past but not HIV co-infection, was associated with INH mono-resistance[2,10,11]. Younger age was commonly observed among patients infected with INH mono-resistant isolates than those harbored susceptible strains[7]. In the present study, as compared to other resistances, history of previously treated was not different, but radiographic cavitary lesion was less likely in those with INH mono-resistance.

Relapse rate in nearly 2,000 patients with INH mono-resistant TB from pooled analysis in the past was around 10-15%. Longer duration of rifampicin and pyrazinamide use seem to lessen failure, relapse, and acquired drug resistance rates[4]. All of the patients with INH mono-resistance pulmonary tuberculosis in the present study who had completed the treatment were cured, and only 1 patient (5%) had disease relapse. This may result from the availability of DST results within an average of 4-6 weeks in our hospital, which guided the early regimen adjustment for physicians accordingly. However, 3 patients without regimen adjustment were also cured. Others studies from different regions, reported the cure rate for INH mono-resistance TB of 90-95%, with the relapse rate of about 5%[5,10-12]. Higher success rate of treatment at

present may result from an availability of early DST and adoption of quinolone-containing regimen for INH mono-resistant TB as suggested by World Health Organization[13]. Current expert opinion from World Health Organization, also suggest to use HRE therapy in the continuation phase rather than HR, for new TB cases in places where high levels of isoniazid resistance exist[14].

Isoniazid-resistant *Mycobacterium tuberculosis* is commonly mediated by katG and inhA genes. However, specific mutations from certain genetic lineages with some phenotypes such as high-level INH-resistance, did not correlate well with clinical presentation and treatment outcome[10,15]. Direct estimates of the proportion for evolution from INH mono-resistant TB to MDR-TB, may not correspond well with some mathematical models[16]. In terms of this phenomenon, we could not demonstrate further resistance in our single relapse case. Spoligotype-based phylogenetic study in Poland also did not fully support the hypothesis of additional acquired resistance in an initial INH mono-resistant TB[17].

The major limitation of the present study is the retrospective nature of the cohort, so some patients were missing, and the treatment regimens could not be controlled. The authors also had a relatively small sample size, and any conclusion drawn from the present study must be further elucidated.

Conclusion

Isoniazid mono-resistant pulmonary tuberculosis patients usually have less cavitary lesions from chest radiograph as compared to those with other resistances. Impact on treatment outcomes may be negligible when the drug susceptibility testing results were available earlier.

What is already known on this topic?

The characteristics of patients with isoniazid mono-resistant pulmonary tuberculosis in Thailand was poorly defined.

What this study adds?

The clinical features of patients with isoniazid mono-resistant pulmonary tuberculosis were not different from other resistances. Excellent treatment outcome can be achieved by timely regimen adjustment according to the drug-susceptibility pattern.

Potential conflicts of interest

None.

References

1. World Health Organization. Global tuberculosis report 2012. WHO/HTM/TB/2012.6. Geneva: WHO; 2012.
2. Hoopes AJ, Kammerer JS, Harrington TA, Ijaz K, Armstrong LR. Isoniazid-monoresistant tuberculosis in the United States, 1993 to 2003. Arch Intern Med 2008; 168: 1984-92.
3. Kasetjaroen Y, Rientong S, Rientong D, Nateniyom S. Antituberculosis drug resistance surveillance round 3 (2006-2007) and the trend of drug resistance in Thailand. Dis Control J 2008; 34: 30-9.
4. Menzies D, Benedetti A, Paydar A, Royce S, Madhukar P, Burman W, et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. PLoS Med 2009; 6: e1000150.
5. Kim YH, Suh GY, Chung MP, Kim H, Kwon OJ, Lim SY, et al. Treatment of isoniazid-resistant pulmonary tuberculosis. BMC Infect Dis 2008; 8: 6. doi: 10.1186/1471-2334-8-6.
6. Falzon D, Jaramillo E, Schunemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J 2011; 38: 516-28.
7. Maguire H, Brailsford S, Carless J, Yates M, Altass L, Yates S, et al. Large outbreak of isoniazid-monoresistant tuberculosis in London, 1995 to 2006: case-control study and recommendations. Euro Surveill 2011; 16. doi:pii: 19830.
8. Forssbohm M, Loddenkemper R, Rieder HL. Isoniazid resistance among tuberculosis patients by birth cohort in Germany. Int J Tuberc Lung Dis 2003; 7: 973-9.
9. Kan B, Berggren I, Ghebremichael S, Bennet R, Bruchfeld J, Chryssanthou E, et al. Extensive transmission of an isoniazid-resistant strain of Mycobacterium tuberculosis in Sweden. Int J Tuberc Lung Dis 2008; 12: 199-204.
10. Bang D, Andersen PH, Andersen AB, Thomsen VO. Isoniazid-resistant tuberculosis in Denmark: mutations, transmission and treatment outcome. J Infect 2010; 60: 452-7.
11. Fox L, Kramer MR, Haim I, Priess R, Metvachuk A, Shitrit D. Comparison of isoniazid monoresistant tuberculosis with drug-susceptible tuberculosis and multidrug-resistant tuberculosis. Eur J Clin Microbiol Infect Dis 2011; 30: 863-7.

12. Cattamanchi A, Dantes RB, Metcalfe JZ, Jarlsberg LG, Grinsdale J, Kawamura LM, et al. Clinical characteristics and treatment outcomes of patients with isoniazid-monoresistant tuberculosis. Clin Infect Dis 2009; 48: 179-85.
13. World Health Organization. Guideline for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2008.402. Geneva: WHO; 2008.
14. World Health Organization. Treatment of tuberculosis: guidelines. 4th ed. WHO/HTM/TB/2009.420. Geneva: WHO; 2009.
15. Dantes R, Metcalfe J, Kim E, Kato-Maeda M, Hopewell PC, Kawamura M, et al. Impact of isoniazid resistance-conferring mutations on the clinical presentation of isoniazid monoresistant tuberculosis. PLoS One 2012; 7: e37956.
16. Dye C, Espinal MA. Will tuberculosis become resistant to all antibiotics? Proc Biol Sci 2001; 268: 45-52.
17. Jagielski T, Augustynowicz-Kopec E, Zozio T, Rastogi N, Zwolska Z. Spoligotype-based comparative population structure analysis of multidrug-resistant and isoniazid-monoresistant Mycobacterium tuberculosis complex clinical isolates in Poland. J Clin Microbiol 2010; 48: 3899-909.

ลักษณะทางคลินิกและผลการรักษาผู้ป่วยวัณโรคปอดจากเชื้อที่ดื้อยาไอโซไนอะซิดชนิดเดียว

นิธิพัฒน์ เจียรกุล, วรชัย แสงทองพินิจ, ศุภร ฟุ้งลัดดา

วัตถุประสงค์: *เพื่อประเมินลักษณะของผู้ป่วยวัณโรคปอดที่เกิดจากเชื้อซึ่งดื้อต่อยาไอโซไนอะซิดชนิดเดียวจากแบบแผนความไวเชื้อต่อยา*

วัสดุและวิธีการ: *ได้ทำการศึกษาแบบย้อนหลังจากเวชระเบียนผู้ป่วยวัณโรคปอดที่เพาะเชื้อได้จากเสมหะและมีผลทดสอบความไวเชื้อต่อยาของโรงพยาบาลศิริราชระหว่างเดือนกรกฎาคม พ.ศ. 2552 ถึง เดือนกรกฎาคม พ.ศ. 2554 โดยรวบรวมข้อมูลพื้นฐาน อาการแสดงทางคลินิก ลักษณะทางรังสีวิทยา แล้วทำการเปรียบเทียบข้อมูล ระหว่างกลุ่มที่ดื้อต่อยาไอโซไนอะซิดอย่างเดียวกับกลุ่มที่ดื้อต่อยาแบบอื่น นอกจากนี้ได้รวบรวมข้อมูลสูตรยาที่ใช้และผลการรักษาสำหรับกลุ่มที่ดื้อต่อยาไอโสไนอะซิดอย่างเดียว*

ผลการศึกษา: *มีผู้ป่วยทั้งหมด 489 ราย ในช่วงเวลาดังกล่าว โดย 28 ราย ตรวจพบเชื้อที่ดื้อต่อยาไอโซไนอะซิดอย่างเดียว คิดเป็นร้อยละ 5.7 ผู้ป่วยกลุ่มนี้มีอายุเฉลี่ย 53±18 ปี ร้อยละ 8 ของผู้ป่วยกลุ่มนี้มีประวัติเคยได้รับการรักษาวัณโรคมาก่อนในอดีต เมื่อเทียบกับกลุ่มผู้ป่วยที่เกิดจากเชื้อดื้อต่อยาแบบอื่นพบภาพถ่ายรังสีทรวงอกก่อนการรักษา มีโพรงแผลน้อยกว่าอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 8.3 เทียบกับ ร้อยละ 26.7, p = 0.006) แต่ไม่แตกต่างกันในด้านข้อมูลพื้นฐานและอาการทางคลินิก ผู้ป่วยทุกรายที่ได้รับการรักษาจนครบพบว่าหายขาด เมื่อเปรียบเทียบระหว่างกลุ่มย่อยที่ได้รับการรักษาด้วยสูตรยาที่มีหรือไม่มีคิวโนโลน พบว่าอัตราการหายขาดและการกลับเป็นซ้ำไม่ต่างกัน*

สรุป: *วัณโรคปอดจากเชื้อที่ดื้อต่อยาไอโซไนอะซิดอย่างเดียวมีลักษณะทางคลินิกไม่แตกต่างจากเชื้อที่ดื้อต่อยาแบบอื่น ยกเว้นพบมีโพรงแผลจากภาพถ่ายรังสีทรวงอกก่อนการรักษาน้อยกว่า การทดสอบความไวของเชื้อต่อยาอย่างเหมาะสมร่วมกับการปรับสูตรยาที่ใช้รักษาอย่างทันท่วงทีสามารถทำให้การรักษาได้ผลดี*