Two Years Review of Cutaneous Adverse Drug Reaction from First Line Anti-Tuberculous Drugs

W C Tan, MD*, C K Ong, MD, S C Lo Kang, MRCP*, M Abdul Razak, FCCP****

*Department of Dermatology, Penang Hospital, ** Respiratory Unit, Penang Hospital, Penang Hospital, Jalan Residensi, 10990, Penang

SUMMARY

First line Anti-TB therapy with rifampicin, isoniazid, pyrazinamide, and ethambutol / streptomycin is very effective. However, major adverse reactions to antituberculous drugs can cause significant morbidity and mortality. Cutaneous adverse drug reaction (CADR) is one of the commonly observed major adverse events. This retrospective study looked at the cases of TB treated in Respiratory Unit, Penang Hospital from January 2004 to December 2005. Of 820 patients treated for active TB, 47 patients (25 females; 22 males) developed CADR (5.7%). CADRs observed include morbiliform rash (72.3%), erythema multiforme syndrome (8.5%), urticaria (8.5%) and others (which include exfoliative dermatitis and lichenoid eruption). Ninety-seven percent of events occurred within two months after the initial dose. Incidence rate of CADR among the first line anti-TB drugs, pyrazinamide was the commonest offending drug (2.38%), followed by streptomycin (1.45%), ethambutol (1.44%), rifampicin (1.23%) and isoniazid (0.98%). Various clinical characteristics of patients with CADR identified include Human Immunodeficiency Virus (HIV) infection (27.7%), polypharmacy (21.3%), elderly (19.1%), autoimmune disorders (6.4%), pre-existing renal impairment (4.3%), pre-existing liver disorders (4.3%). In conclusion, CADR is common and majority of cases occurred within two months after initiation of anti-TB treatment, particularly in HIV infected patients. Pyrazinamide is the commonest offending drug.

KEY WORDS:
Antituberculosis, Cutaneous Adverse Drug Reaction, Tuberculosis.

INTRODUCTION

First line anti-tuberculous (anti-TB) therapy with rifampicin, isoniazid, pyrazinamide and ethambutol/streptomycin is very effective[1]. A major adverse reaction to one of the first line antituberculous drugs, which results in discontinuation of that drug, has several implications and complicate the anti-TB treatment. There may be considerable morbidity, even mortality, particularly with severe cutaneous adverse drug reaction (CADR)[1-2]. CADR is one of the commonly observed side effects[1-4]. CADR is defined as skin reactions secondary to systemic administration of drugs (oral/subcutaneous/ intravenous/intramuscular/inhalation). It has been well established that anti-TB drug are among the commonest drug that cause cutaneous drug reactions[3-5]. Identification of patients with risk factors will facilitate monitoring of major adverse effect from anti-TB.

MATERIALS AND METHODS

This retrospective study looked at the cases of adult active TB treated in Respiratory Unit, Penang Hospital from January 2004 to December 2005. The information were obtained from patients' medical report, TB booklet and in-patient record (if they had been admitted previously). Demographic characteristic, causative drug and management were recorded and analysed.

The objectives of this study are:

- To determine the pattern of CADR that is commonly associated with anti-TB therapy.
- To determine the drug(s) that commonly cause CADR in patients treated for TB.
- To identify the clinical characteristics of patients who developed CADR.

All the cases of adult active TB treated with 1st line anti-TB drug in Respiratory Unit, Penang Hospital in 2004-2005 were included in the study. Diagnosis of cutaneous ADR will be based on clinical impression and relevant investigations including a skin biopsy when deemed necessary by the dermatologist.

A drug was defined as responsible for CADR if symptoms and signs resolved after withdrawal and recurred after re-challenge with that drugs. Attribution was also made if the cutaneous adverse drug reaction resolved with discontinuation of the drug, even without re-challenge.

Inclusion criteria:

- Clear history of drug induced reaction.
- De-challenge improves the skin condition.

Exclusion criteria:

- Absence of a causative drug according to our definition.
- Lack of recorded date when the causative drug was started/ stopped or disease evolution.
- Skin disorder attributable to infection.

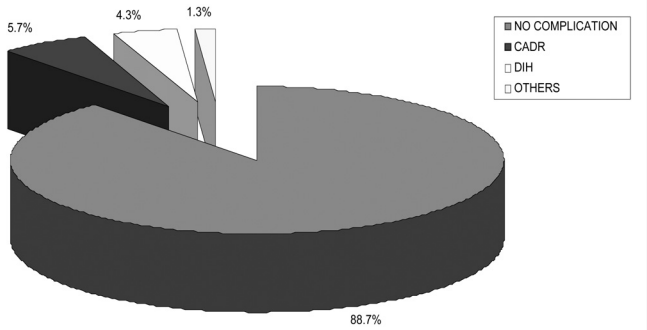
RESULTS

Of a total of 820 patients (Mean age of study population: 45.8 ± 16.2 years; range from 13 years to 91 years) treated for TB, 47 patients developed CADR (5.7%). There were 25 females

This article was accepted: 9 May 2007
Corresponding Author: Tan Wooi Chiang, Department of Dermatology, Penang General Hospital, 10990 Penang

and 22 male patients (22 Chinese, 15 Malay; 6 Indian and 4 foreigners). 46.8% of patients who developed CADR were of 35-59 years of age. Demographic characteristic of patients were shown in Figures 1 and 2. The common pattern of CADR observed include morbiliform rash (34, 72.3%); erythema multiforme syndrome (4, 8.5%), urticaria (4, 8.5%) and others which include exfoliative dermatitis, lichenoid eruption and others (Refer to Figure 3).

With regards to the onset of cutaneous ADR in relation to the TB treatment, we observed that CADR occurred within two months of initiation of treatment in 97% of patients. In our observation, we noted that all the patients who developed CADR had itchiness and cutaneous eruption. 17.0% of patients had a more serious reaction, which include facial swelling, epidermal detachment and mucosal involvement. With regards to the extent of cutaneous ADR, majority of patients were classified as mild involvement, of which the body surface area (BSA) involvement was < 10%. Those with BSA 10-30% were categorized as moderate. Four patients developed severe CADR with BSA of > 30% or with signs and symptoms of severe CADR.



CADR = Cutaneous Adverse Drug Reaction; DIH = Drug Induced Hepatitis

Fig. 1: Number of tuberculosis cases treated at respiratory unit, Penang Hospital 2004-2005.

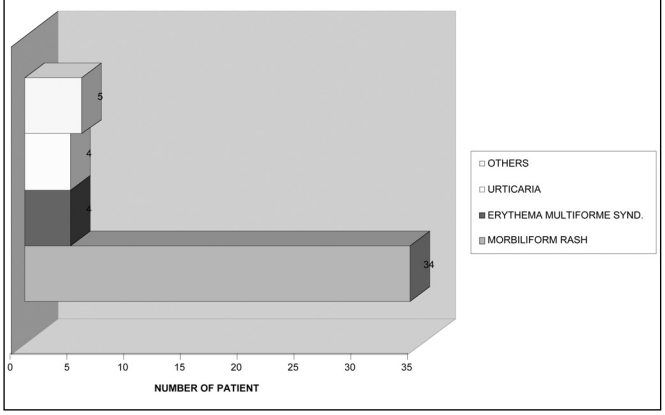


Fig. 3: Type of CADR developed secondary to Anti-TB treatment in respiratory unit, Penang Hospital 2004-2005.

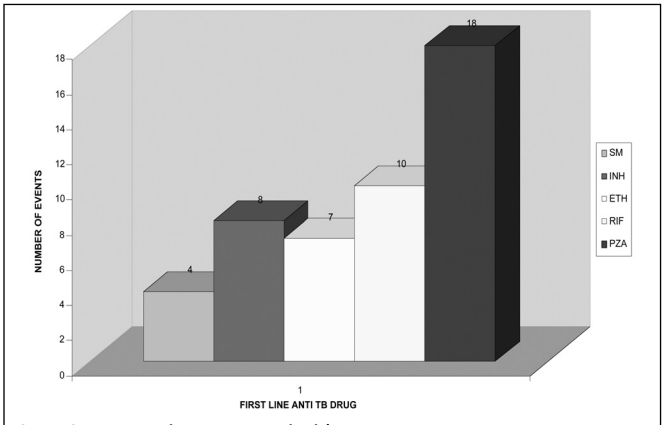
In our study, we noted that pyrazinamide was the commonest offending drugs (38.3%), followed by rifampicin (21.3%), isoniazid (17.0%), ethambutol (14.9%) and streptomycin (8.5%). But looking at CADR adverse event per total usage of a particular anti-TB drug (incidence rate), the commonest causative drugs were pyrazinamide (2.38%), followed by streptomycin (1.45%), ethambutol (1.44%), rifampicin (1.23%) and isoniazid (0.98%). (Figures 4 and 5) Among the patients with CADR, 70.3% were managed as out-patient, 29.7% requires hospitalization. 73.0% of patients had their anti-TB regimen modified secondary to cutaneous ADR. 14.8% of patients needed to be desensitized. In our study population, clinical characteristics identified include HIV infection (27.7%), poly-pharmacy (21.3%), elderly (19.1%), autoimmune disorders (6.4%), pre-existing renal impairment (4.3%), pre-existing liver disorders (4.3%). But in our series, only HIV infection, poly-pharmacy and autoimmune disorders reveal obvious correlation with CADR. (Figure 6)

DISCUSSION

CADR is commonly observed in patients treated with anti-TB drugs[1-10]. CADR can mimic all the morphologic expressions in

Fig. 2: Characteristics of TB Patients Who developed CADR in respiratory Unit, Penang Hospital 2004-2005

	n	%
Total CADR	47	5.7
SEX		
• Male	22	46.8
• Female	25	53.2
AGE		
• 13-34 yrs	16	34.0
• 35-59 yrs	22	46.8
• > 60 yrs	9	19.2
ETHNIC		
• Malay	15	31.9
• Chinese	22	46.8
• Indian	6	12.8
• Others	4	8.5
HIV STATUS		
• +VE	13	27.7
• -VE	34	72.3
• Not Available	0	0



SM = Streptomycin; INH = Isoniazid; ETH = Ethambutol; RIF = Rifampicin; PZA = Pyrazinamide

Fig. 4: Common offending agent(s) indentified (First line Anti-TB).

Fig. 5: Incidence Rate of CADR among 1st line antituberculous drug

DRUG	SM	INH	ETH	RIF	PZA
N	276	820	485	816	757
N(CADR)	4	8	7	10	18
Incidence Rate (%)	1.45	0.98	1.44	1.23	2.38

SM = Streptomycin; INH = Isoniazid; ETH = Ethambutol; RIF = Rifampicin; PZA = Pyrazinamide

Fig. 6: Clinical characteristics and their Correlation With CADR among the study population

		CADR		
		YES (N)	NO (N)	P
HIV Infection	Yes	13	90	0.001
	No	34	683	
Poly-pharmacy	Yes	10	64	0.003
	No	37	709	
Autoimmune Disorder	Yes	3	2	<0.001
	No	44	771	
Pre-existing Renal Impairment	Yes	2	39	NS
	No	45	734	
Pre-existing Liver Disorder	Yes	2	35	NS
	No	45	738	
Elderly	Yes	9	172	NS
	No	38	601	

dermatology[4]. Drug eruption must be considered as one of the differential diagnosis of a suddenly appearing symmetric eruption. This is especially true for those with high risk like elderly[2, 4, 11], patients with organ failure[4], poly-pharmacy (use of more than 5 types of medication excluding anti-TB drug)[4, 12-13], patients with certain infections (HIV, EBV, TB)[2, 4, 6, 12-13], patients with certain autoimmune diseases (Rheumatoid arthritis, Sjogren's disease or Systemic Lupus Erythematosus)[4, 14], patients with malignancy especially haematological malignancy[4] and genetic susceptibility[9, 15]. However in our series, factors like elderly, patient with organ failure did not reveal obvious correlation with CADR. This is probably due to the small sample size and study design (retrospective study). Our study showed that pyrazinamide is the most common offending agent that causes CADR. The similar studies done in various centers looking at the adverse event secondary to anti-TB in general, and drug rash in particular, have also shown the same findings. Our results are in agreement with those of the series[2, 4, 7-8]. CADR usually occurred within two months of initiation of drug therapy[2, 4-5, 16]. The management of TB patient with CADR depends on its severity. If CADR is mild topical corticosteroid and antihistamine can be given and the anti-TB drugs can be continued under close clinical monitoring. These patients can be managed as out-patient but close follow up is recommended[1, 17-18]. All drugs should be stopped immediately when there is a generalized erythematous rash, especially if it is associated with signs and symptoms of severe CADR[1, 17-18] (such as facial oedema, skin pain, palpable purpura, skin necrosis, blisters, epidermal detachment, positive Nikolsky's sign, mucous membrane erosions, high grade fever or hypotension)[4]. Hospitalization and close monitoring is required in these cases. When the rash substantially improved, the medications can be re-challenged one by one, at intervals of 2-3 days[1, 17-18].

The re-challenge should always start with the drug that is the least likely to cause rash, i.e. rifampicin, followed by isoniazid, ethambutol and pyrazinamide[1, 17-18]. Challenge should be done for one drug at one time. If no rash appears after the first three drugs have been restarted, the 4th drug should not be started unless the rash was relatively mild and the 4th drug is considered essential for therapy[1]. Rechallenge should not be performed after a serious reaction. Reactions after rechallenge may be worse. Desensitization is only indicated if no other alternative or suitable drug combination is available (i.e. patient is allergic to isoniazid and/or rifampicin). Desensitization is done by careful daily administration of increasing doses of the drug under close supervision until the therapeutic dose is reached[1, 17-18]. During desensitization, systemic corticosteroid may be used. Management of CADR involves a multi-disciplinary approach[19-20]. Early diagnosis and prompt withdrawal of the suspected offending medication is crucial[21]. Notification is important[22-23]. Allergy card should be given to patient.

Supportive treatment is essential in the management of CADR. Systemic steroids should only be used in severe or generalized erythematous rash or rash associated with angioedema. The use of systemic corticosteroids in Stevens-Johnson syndrome or Toxic Epidermal Necrolysis remains controversial. Most of the studies showed that it is harmful (may results in a higher incidence of complication)[4-5, 24-25].

In conclusion, diagnosis of CADR requires a high index of suspicion especially in those having symmetrical eruption within two months in relation to initial dose of anti-TB, particularly HIV infected patients. Although it is important to be attuned to the potential for adverse effects it is at least equally important that 1st line anti-TB drug not be stopped without adequate justification.

ACKNOWLEDGEMENTS

We are most grateful to all the staffs of Respiratory Unit, Penang General Hospital for their help in collecting and compounding data.

REFERENCES

1. Official Joint Statement of the American Thoracic Society, Center for Disease Control and Prevention, and the Infectious Diseases Society of America on Treatment of Tuberculosis 2002.
2. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of Serious Side Effects from 1st Line Anti-tuberculosis Drugs among Patients Treated for Active Tuberculosis. Am J Respir Crit Care Med 2003; 167: 1472-77.
3. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. JAMA 1986; 256: 3358-63.
4. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. New Engl J Med 1994; 331: 1272-85.
5. Roujeau JC, Kelly JP, Naldi L, *et al*. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. New Engl J Med 1995; 333: 1600-607.
6. Chan HL, Stern RS, Arndt KA, *et al*. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: a population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol 1990; 126: 43-47.
7. Ormerod LP, Harsfield N. Frequency and Type of Reactions toAnti-tuberculous Drugs: Observation in Routine Treatment. Tuber Lung Dis 1996; 77: 37-42.
8. American Thoracic Society. Treatment of TB and TB Infection in Adults and Children. Am Rev Respir Dis 1994; 149: 1359-74.
9. Roujeau JC, Huynh TN, Bracq C, Guillaume JC, Revuz J, Touraine R. Genetic Susceptibility to Toxic Epidermal Necrolysis. Arch Dermatol 1987; 123: 1171-73.
10 Jordan MH, Lewis MS, Jeng JG, Rees JM. Treatment of toxic epidermal necrolysis by burn units: another market or another threat? J Burn Care Rehabil 1991; 12: 579-81.
11. Tristani-Firouzi P, Petersen MJ, Saffle JR, *et al*. Treatment of toxic epidermal necrolysis with intravenous immunoglobulins in children. J Am Acad Dermatol 2002; 47: 548-52.
12. Saiag P, Caumes E, Chosidow O, Revuz J, Roujeau JC. Drug-induced toxic epidermal necrolysis (Lyell syndrome) in patients infected with the human immunodeficiency virus. J Am Acad Dermatol 1992; 26: 567-74.
13. Rzany B, Mockenhaupt M, Stocker U, Hamouda O, Schopf E. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with the acquired immunodeficiency syndrome in Germany. Arch Dermatol 1993; 129: 1059-59.
14. Burge SM, Dawber RPR. Stevens-Johnson syndrome and toxic epidermal necrolysis in a patient with systemic lupus erythematosus. J Am Acad Dermatol 1985; 13: 665-66.
15. Roujeau JC, Huynh TN, Bracq C, Guillaume JC, Revuz J, Touraine R. Genetic susceptibility to toxic epidermal necrolysis. Arch Dermatol 1987; 123: 1171-73.
16. Revuz J, Penso D, Roujeau JC, *et al*. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. Arch Dermatol 1987; 123: 1160-65.
17. World Health Organization, Treatment of Tuberculosis: Guidelines for National Programmes, 1997 (Second Edition).
18. Practice Guidelines for the Control and Management of Tuberculosis, 2nd Edition 2002, Ministry of Health Malaysia.
19. Engelhardt SV, *et al*. Toxic epidermal necrolysis: An analysis of referral patterns and steroid usage. J Burn Care Rehabil 1997; 18: 520-24.
20. Wilkins J, Morrison L, White CR Jr. Oculocutaneous manifestations of the erythema multiforme / Stevens-Johnson syndrome / toxic epidermal necrolysis spectrum. Dermatol Clin 1992; 10: 571-582.
21. Ignacio Garcia-Doral, *et al*. Toxic epidermal necrolysis and Stevens-Johnson syndrome: Does early withdrawal of causative drug decrease the risk of death? Arch Dermatol 2000; 136: 323-27.
22. Kessler DA. Introducing MED Watch: a new approach to reporting medication and device adverse effects and product problems. JAMA 1993; 269: 2765-68.
23. Moore N, Biour M, Paux G, *et al*. Adverse drug reaction monitoring: doing it the French way. Lancet 1985; 2: 1056-58.
24. Halebian PH, Corder VJ, *et al*. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroid. Ann Surg 1986; 204: 503-12.
25. Stern RS. Improving the outcome of patients with toxic epidermal necrolysis and Stevens-Johnson syndrome. Arch Dermatol 2000; 136: 410-11.