PREVALENCE AND RISK FACTORS OF ANTITUBERCULOSIS DRUG-INDUCED HEPATITIS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

By

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LIST OF ABBREVIATIONS

AFB	acid-fast bacilli
AIDS	Acquired Immuno-deficiency Syndrome
ALT	alanine aminotransferase
ALP	alkaline phosphatase
Anti-TB	antituberculosis
ARDS	Adult Respiratory Distress Syndrome
AST	aspartate aminotransferase
ATS	American Thoracic Society
CDC	Centers for Disease Control and Prevention, United States of America
CI	confidence interval
CT	computed tomography
dl	decilitre
HBeAg	hepatitis B envelope antigen
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IU	international unit
L	litre
mg	milligram
mm	millimeter
MMWR	Morbidity and Mortality Weekly Report
M. tuberculosis	*Mycobacterium tuberculosis*
MRI	magnetic resonance imaging

PPD	purified protein derivatives
TB	tuberculosis
ULN	upper limit of normal
WHO	World Health Organization
μmol	micromol

ABSTRAK

Latar belakang

Tuberkulosis merupakan satu daripada penyakit utama dunia, membabitkan kira-kira satu pertiga daripada penduduk dunia. Pengenalan ubat antituberkulosis beberapa dekad yang lalu telah memperbaiki nasib pesakit yang dijangkiti tuberculosis dengan sebaiknya. Di antara ubatan antituberkulosis, isoniazid, rifampicin dan pyrazinamide telah terbukti berkesan, tetapi bukan tanpa kesan sampingan, seperti keracunan hati. Hepatitis disebabkan ubat antituberkulosis telah banyak dilaporkan dan banyak faktor-faktor risiko telah dikesan.

Objektif

Kajian kes kawalan dan pemerhatian ini dijalankan untuk memastikan kewujudan hepatitis disebabkan ubat antituberkulosis di Hospital Universiti Sains Malaysia, memastikan faktor-faktor risiko hepatitis disebabkan ubat antituberkulosis dan memerhati perkembangan klinikal pesakit yang menghidapi hepatitis.

Metod

Kajian ini memeriksa bukti-bukti hepatitis disebabkan ubat antituberkulosis di kalangan pesakit yang dirawat sebagai tuberkulosis di Klinik Dada sepanjang 30 bulan daripada Januari 2003 hingga Jun 2005. Kes-kes hepatitis disebabkan ubat antituberkulosis yang layak dipilih dan dibandingkan dengan pesakit kawalan yang dipilih secara Sampel Rawak Mudah dari segi data demografi dan faktor risiko yang terlibat seperti umur, jantina, indeks jisim badan, pembawa hepatitis B, jangkitan HIV, tempat tuberkulosis dan fungsi biokimia hati seperti albumin, globulin, AST, ALT dan bilirubin. Perkembangan klinikal pesakit yang menghidapi hepatitis diperiksa dari segi

permulaan, keterukan dan jangkamasa hepatitis serta adanya jaundis. Data dianalisis menggunakan khi square dan ujian *t* bebas (univariasi) dan analisis regresi binari logistik (multivariasi).

Keputusan

Sejumlah 473 pesakit didaftarkan sepanjang tempoh kajian, 46 orang daripadanya dikesan menghidapi hepatitis disebabkan ubat antituberkulosis dan layak untuk kajian. 138 pesakit lain dipilih sebagai kawalan. Prevalens hepatitis disebabkan ubat ialah 9.7 peratus. Daripada faktor-faktor risiko yang dianalisis, jangkitan HIV (p=0.05) dan tuberkulosis ekstrapulmonari (p=0.008), tahap albumin serum rendah (p=0.023) dan tahap globulin tinggi (p=0.025) dikesan signifikan dalam analisis univariasi. Dalam analisis regresi logistik binari, jangkitan HIV (p=0.018) dan tuberkulosis ekstrapulmonari (p=0.017) dikesan sebagai faktor risiko yang signifikan. Pemerhatian perkembangan klinikal pesakit yang mengalami hepatitis menunjukkan kebanyakannya menghidapi hepatitis ringan (58.7%) dan sederhana (32.6%). Permulaan hepatitis kebanyakannya berlaku dalam satu hingga dua minggu (32.6%) dan dua hingga tiga minggu (17.4%). Tempoh hepatitis kebanyakannya dalam masa seminggu (34.8%) sehingga dua minggu (32.6%). Jaundis berlaku kepada 32.6 peratus pesakit.

Rumusan

Prevalens hepatitis disebabkan ubat antituberkulosis ialah 9.7 peratus. Jangkitan HIV dan tuberkulosis ekstrapulmonari merupakan faktor-faktor risiko terjadinya hepatitis. Kebanyakan pesakit mengalami simptom dan tanda hepatitis yang ringan. Pesakit yang mempunyai faktor risiko perlu diperhati secara teliti berkaitan terjadinya hepatitis disebabkan ubat antituberkulosis.

ABSTRACT

Background

Tuberculosis is one of the major diseases worldwide, affecting about one-third of the world's population. The introduction of antituberculosis drugs decades ago has improved tremendously the outcome of those infected with tuberculosis. Among the drugs, isoniazid, rifampicin and pyrazinamide had been proven to be effective, but not without the side effects, of which hepatotoxicity is the most important. Antituberculosis drug-induced hepatitis has been reported and many risk factors had been recognized.

Objectives

This case control and observational study was conducted to determine the prevalence of antituberculosis drug-induced hepatitis in Hospital Universiti Sains Malaysia, to determine the risk factors in relation to the development of drug-induced hepatitis as well to observe the clinical course in patients with antituberculosis drug-induced hepatitis.

Method

This study examined the evidence of antituberculosis drug-induced hepatitis in patients treated for tuberculosis in Chest Clinic for a period of 30 months from January 2003 until June 2005. Eligible cases of drug-induced hepatitis were selected and compared with controls which were selected by Simple Random Sampling in terms of demographic data and risks involved such as age, gender, body mass index, hepatitis B carrier, HIV infection, sites of tuberculosis, and pretreatment liver biochemistries such as serum albumin, globulin, AST, ALT and bilirubin. The clinical course of patients of hepatitis was also examined in term of onset, severity and duration of hepatitis, as well

as the presence of jaundice. Data were evaluated by khi square and independent *t* test (univariate) and binary logistic regression analysis (multivariate).

Results

A total of 473 patients were registered during the period of the study, 46 patients were noted to have antituberculosis drug-induced hepatitis and eligible for the study. 138 patients were selected as controls. The prevalence of drug-induced hepatitis was 9.7%. Among the risk factors evaluated, the presence of HIV infection (p=0.05), extrapulmonary tuberculosis (p=0.08), lower serum albumin (p=0.023) and higher serum globulin (p=0.025) were noted to be significant at univariate analysis. On binary logistic regression analysis, the presence of HIV infection (p=0.018) and extrapulmonary tuberculosis (p=0.017) were noted to be significant risk factors. Observation of the clinical course of patients who had drug-induced tuberculosis, showed that most of them had mild hepatitis (58.7%) and moderate hepatitis (32.6%). The onset of hepatitis mostly occurred between one to two weeks (32.6%) and two to three weeks (17.4%). The duration of hepatitis was mostly from one week (34.8%) to two weeks (32.6%). The occurrence of jaundice was 32.6 percent.

Conclusion

The prevalence of antituberculosis drug-induced hepatitis was 9.7 percent. The presence of HIV infection and extrapulmonary tuberculosis were significant risk factors for the development of hepatitis. Most of the patients who developed antituberculosis drug-induced hepatitis had mild symptoms and signs. Patients with risk factors should be monitored closely for the development of drug-induced hepatitis.

CHAPTER ONE

INTRODUCTION

1. INTRODUCTION

1.1 Tuberculosis

1.1.1 Background

Tuberculosis, one of the oldest diseases known to affect humans, is caused by bacteria belonging to the *Mycobacterium tuberculosis* complex. The disease usually affects the lungs, although, in up to one-third of cases other organs are also involved. Transmission usually takes place through air-borne spread of droplet nuclei produced by patients with infectious pulmonary tuberculosis (Kasper DL *et al*, 2005).

1.1.2 Aetiologic Agent

Mycobacteria belong to the family Mycobacteriaceae and the order Actinomycetales. Among the pathogenic species belonging to the *M. tuberculosis* complex, the most frequent and important agent of human disease is *M. tuberculosis*. The complex includes *M. bovis*, *M. africanum*, *M. microti* and *M. canettii*.

M. tuberculosis is a rod-shaped, non-spore forming, thin aerobic bacterium and is often neutral on Gram's staining. However, once stained, the bacilli cannot be decolourized by acid alcohol, a characteristic called 'acid-fast bacilli'. Acid fastness is due mainly to the organisms' high content of mycolic acid, long-chain cross-linked fatty acids, and other cell-wall lipids (Kasper DL *et al*, 2005).

1.1.3 Epidemiology

Tuberculosis is a worldwide pandemic. In recent years the incidence of tuberculosis has been rising, ranking this disease as one of the major threats to public health (Snider DE & Roper WL, 1992).

In 2003, 8.8 million new tuberculosis cases were reported globally. Overall, one third of the world's population is currently infected with *M. tuberculosis* with global incidence growing at one percent per year. Nearly two million deaths are reported every year due to tuberculosis, with most of them (98%) occurring in the developing world affecting mostly young adults in their most productive years (WHO, 2005).

The largest number of cases occur in the South-East Asian Region, which accounts for 33 percent of the global prevalence. However, the estimated incidence per capita in sub-Saharan Africa is nearly twice that of South-East Asia, at 350 cases per 100,000 population (WHO, 2005).

In Malaysia, for the year 1999, 14,908 new cases of tuberculosis were reported, with the majority of them occurring in the economically productive age group (15-50 years old) (Ministry of Health Malaysia, 2002). Latest estimates put Malaysia in the 46th place in the global rank by number of cases of tuberculosis. The incidence of new cases of tuberculosis is currently 47 per 100,000 population per year, with prevalence of all cases of 136 cases per 100,000 population. The tuberculosis mortality rates in Malaysia were estimated at 17 cases per 100,000 population per year (WHO, 2005).

1.1.4 Pathogenesis

The interaction of *M. tuberculosis* with the human host begins when droplet nuclei containing microorganisms from infectious patients are inhaled. While the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually less than 10%) reach the alveoli, where the bacilli are ingested by activated alveolar macrophages.

In the initial stage of host-bacterium interaction, either the host's macrophages contain bacillary multiplication by producing proteolytic enzymes and cytokines, or the bacilli begin to multiply. If the bacilli multiply, their growth quickly kills the macrophages. Nonactivated monocytes later ingest the bacilli released from the lysed macrophages. These initial stages of infection are usually asymptomatic.

About two to four weeks after infection, two additional host responses to *M. tuberculosis* develop: a tissue-damaging response as a result of a delayed-type hypersensitivity reactions to various bacillary antigens which destroys nonactivated macrophages that contain multiplying bacilli; and a macrophage-activating response that is a cell-mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. The balance between these two factors determines the form of tuberculosis that will develop subsequently (Kasper DL *et al*, 2005).

1.1.5 Clinical Manifestations

Tuberculosis is classified as pulmonary or extrapulmonary depending upon the sites involved.

1.1.5(a) Pulmonary Tuberculosis

Pulmonary tuberculosis can be categorized as primary or postprimary (secondary).

1.1.5(a)(i) Primary Disease

Primary pulmonary tuberculosis results from an initial infection with the tuberculosis bacilli. The lesion is usually situated peripherally either in the middle or lower lung zones and accompanied by hilar or paratracheal lymphadenopathy, which may not be detected radiographically. In the majority of cases, the lesion heals spontaneously and may later develop a small calcified nodule, the Ghon lesion.

In children and immunocompromised patients, primary pulmonary tuberculosis may progress rapidly to develop several clinical manifestations such as pleural effusion, cavitation as well as hilar or mediastinal lymphadenopathy causing obstruction and subsequent lung collapse. Haematogenous spread may disseminate into various organs, where they may produce granulomatous lesions. Immunocompromised patients may later develop miliary tuberculosis and tuberculous meningitis (Kasper DL *et al*, 2005).

1.1.5(a)(ii) Postprimary Disease

Postprimary disease results from endogenous reactivation of latent infection and is usually localized to the apical and posterior segments of the upper lobes, where the high oxygen concentration favours mycobacterial growth. The superior segments of the lower lobes are also frequently involved. The extent of lung parenchymal involvement varies, from small infiltrates to extensive cavitary disease.

Early manifestations are often non-specific and insidious, consisting mainly of fever, night sweats, weight loss, anorexia and malaise. In the majority of cases, cough eventually develops, initially non-productive and subsequently purulent, with haemoptysis frequently documented.

Physical findings may reveals crepitations and rhonchi over affected areas but frequently no abnormality would be detected. Haematologically, there would be mild anaemia with leucocytosis (Kasper DL *et al*, 2005).

1.1.5(b) Extrapulmonary Tuberculosis

This is mainly due to lympho-haematogenous dissemination during primary tuberculosis infection. The most commonly involved sites in extrapulmonary tuberculosis are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, gastrointestinal and peritoneum, as well as pericardium. However, virtually all organ systems may be affected (Kasper DL *et al*, 2005). Symptoms are often non-specific, including lassitude, anorexia, fever, and weight loss. Specific features will relate to the organs involved.

1.1.5(b)(i) Tuberculous Lymphadenitis

Tuberculous lymphadenitis is the most common presentation of extrapulmonary tuberculosis (documented in more than 25% of cases) and particularly frequent among HIV-infected patients.

It presents as painless swelling of lymph nodes, most commonly at cervical and supraclavicular sites. Systemic symptoms are usually limited to HIV-infected patients. The diagnosis is established by fine-needle aspiration or surgical biopsy. AFB are seen in up to 50 percents of cases, cultures are positive in 70-80 percents, and histologic examination shows granulomatous lesions (Kasper DL *et al*, 2005).

1.1.5(b)(ii) Pleural Tuberculosis

Pleural tuberculosis results from penetration by tuberculosis bacilli into the pleural space. Symptoms such as fever, pleuritic chest pain and dyspnoea may occur, depending upon the extent of reactivity. Clinical and chest radiograph findings are those of pleural effusion.

Thoracocentesis is required to ascertain the nature of the effusion. AFB are very rarely seen on direct smear, but cultures may be positive for *M. tuberculosis* in up to one-third of cases. Pleural biopsy is often required for diagnosis and may reveal granulomas. It may yield a positive culture in up to 70 percents of cases (Kasper DL *et al*, 2005).

1.1.5(b)(iii) Tuberculosis of the Upper Airways

Tuberculosis of the upper airways may involve the larynx, pharynx and epiglottis, and nearly always a complication of advanced cavitary pulmonary tuberculosis. Symptoms include hoarseness, dysphagia as well as chronic productive cough. Sputum for AFB is often positive, but biopsy may be necessary in some cases to establish the diagnosis (Kasper DL *et al*, 2005).

1.1.5(b)(iv) Genitourinary Tuberculosis

This accounts for approximately 15 percent of all extrapulmonary tuberculosis and is usually due to haematogenous seeding following primary infection. Common presentations are urinary frequency, dysuria, haematuria and flank pain, but patient may be asymptomatic. Urinalysis reveals pyuria and haematuria in nearly 90 percent of the cases. The documentation of culture-negative pyuria in acidic urine raises the suspicion of tuberculosis.

Genital tuberculosis is more common in female, which affects the fallopian tubes and endometrium, and may cause infertility, pelvic pain as well as menstrual abnormalities. Diagnosis requires biopsy or culture of specimens obtained by dilatation and curettage. In male patients, the epididymis is often affected (Kasper DL *et al*, 2005).

1.1.5(b)(v) Skeletal Tuberculosis

Tuberculosis of the bones and joints is responsible for approximately 10 percent of extrapulmonary cases. It is related to reactivation of haematogenous foci or to spread from adjacent paravertebral lymph nodes. Weight-bearing joints (spines, hips and knees) are commonly affected. It may produce pain and swelling at the affected site.

Diagnosis is confirmed by aspiration of the abscess or bone biopsy as cultures are usually positive and histologic findings highly typical. Computed tomography (CT) scan and magnetic resonance imaging (MRI) reveals the characteristic lesion and may suggest its aetiology (Kasper DL *et al*, 2005).

1.1.5(b)(vi) Tuberculous Meningitis

Tuberculous meningitis accounts for five percent of extrapulmonary cases, seen most often in young children but also develop in adults, especially those who are infected with HIV. Tuberculous meningitis results from the haematogenous spread of primary or post-primary pulmonary disease or from rupture of a subependymal tubercle into the subarachnoid space. It may present subtly as headache and mental changes, or acutely as confusion, altered sensorium and neck rigidity.

Lumbar puncture is the cornerstone of diagnosis and examination of cerebrospinal fluid (CSF) may reveal high leukocyte count and protein level with a low glucose concentration. AFB are seen on direct smear in 20 percent of cases, culture of CSF is positive in up to 80 percent of cases (Kasper DL *et al*, 2005).

1.1.5(b)(vii) Gastrointestinal Tuberculosis

Any portion of gastrointestinal tract may be affected by tuberculosis. Various pathogenetic mechanisms can be involved such as swallowing of sputum with direct seeding, haematogenous spread or rarely ingestion of bovine tuberculosis-infected milk. It commonly involves the terminal ileum and the caecum. The presentation includes abdominal pain, diarrhoea, haematochezia as well as fever, weight loss and night sweats. The diagnosis is usually by histologic examination and culture of specimens involved.

Tuberculous peritonitis follows either the direct spread of tubercle bacilli from ruptured lymph nodes and intraabdominal organs or haematogenous seeding. Symptoms include nonspecific abdominal pain, fever and ascites. Paracentesis reveals an exudative

fluid with a high protein content and leucocytosis that is usually lymphocytic. The yield of direct smear and culture is relatively low, hence peritoneal biopsy may be required to establish the diagnosis (Kasper DL *et al*, 2005).

1.1.5(b)(viii) Pericardial tuberculosis

This is either due to direct progression of a primary focus within the pericardium, reactivation of a latent focus or to a rupture of adjacent lymph nodes, which is frequently seen in HIV-infected patients. The onset may be subacute, although an acute presentation of fever, dull retrosternal pain and a friction rub is also possible. Pericardial effusion develops in many cases.

Diagnosis is by pericardiocentesis, which may reveal haemorrhagic, exudative and high leukocytes effusion. Culture is positive in about 30 percent of cases, while biopsy has a higher yield (Kasper DL *et al*, 2005).

1.1.5(b)(ix) Miliary Tuberculosis

Miliary or disseminated tuberculosis is due to haematogenous spread of tuberculosis bacilli either due to recent infection or reactivation of old disseminated foci. Lesions are usually yellowish granulomas one to two mm in diameter that resemble millet seeds. Symptoms are non-specific and usually include fever, night sweats, anorexia and weight loss. Others may have respiratory or abdominal symptoms. Physical findings include hepatomegaly, splenomegaly, and lymphadenopathy. Fundoscopy may reveal choroidal tubercle in up to 30 percent of cases.

Chest radiograph may reveal a miliary reticulonodular pattern as well as large infiltrates, interstitial infiltrates and pleural effusion. A sputum smear is negative in 80 percent of cases and Mantoux test may be negative in up to 50 percent of cases. Bronchoalveolar lavage and transbronchial, liver or bone marrow biopsy may give higher yield (Kasper DL *et al*, 2005).

1.1.5(c) HIV-Associated Tuberculosis

Tuberculosis is an important opportunistic disease among HIV-infected patients worldwide. It can appear at any stage of HIV infection and its presentation varies with the stage. In partially immunocompromised patient, it presents as a typical pattern of upper lobe infiltrates and cavitation. In later stages, a primary tuberculosis-like pattern with diffuse interstitial or miliary infiltrates and intrathoracic lymphadenopathy, is more common.

Extrapulmonary tuberculosis is common among HIV-infected patients. In various series, extrapulmonary tuberculosis – alone or in association with pulmonary disease – has been documented in 40 to 60 percent of all cases in HIV co-infected patients. The most common forms are lymphatic, disseminated, pleural and pericardial as well as meningitis.

The diagnosis of tuberculosis in HIV-infected patients may be difficult not only because of the increased frequency of sputum-smear negativity but also because of atypical radiographic findings, a lack of classic granuloma formation in the late stages and negative result in PPD skin tests (Kasper DL *et al*, 2005).

1.1.6 Diagnosis

Diagnosis of tuberculosis is based on clinical, radiological and/or bacteriological evidence.

1.1.6(a) AFB Microscopy

This is based on the finding of AFB on microscopic examination of a diagnostic specimen such as sputum or tissue e.g. lymph node biopsy.

1.1.6(b) Mycobacterial Culture

Definitive diagnosis depends on the isolation and identification of *M. tuberculosis* from a diagnostic specimen, usually sputum. Because most species of mycobacteria including *M. tuberculosis* grow slowly, four to eight weeks may be required before growth is detected.

1.1.6(c) Nucleic Acid Amplification

This is based on amplification of mycobacterial nucleic acid. However, it is limited by low sensitivity and high cost.

1.1.6(d) Radiography

Classic picture of tuberculosis on chest x-ray is upper lobe infiltrates with cavitation. However, virtually any radiographic pattern – from a normal film or a solitary pulmonary nodule to diffuse alveolar infiltrates in a patient with Adult Respiratory Distress Syndrome (ARDS) – may be seen. In the era of AIDS, no radiographic pattern can be considered pathognomonic.

1.1.6(e) PPD Skin Test

This test is used as a screening test for *M. tuberculosis* infection, but it is limited by its low sensitivity and specificity. False negative reactions are common in immunocompromised patients and in those with overwhelming tuberculosis. Positive reactions are seen in patients infected with *M. tuberculosis* and those who have been sensitized by nontuberculous mycobacteria or bacille Calmette-Guérin (BCG) vaccination.

1.1.6(f) Other Diagnostic Procedures

Other diagnostic procedures might be required in order to diagnose tuberculosis. This include bronchoscopy with bronchial brushings, bronchoalveolar lavage or transbronchial biopsy.

For patients suspected to have extrapulmonary tuberculosis, specimens from the involved sites may be required such as cerebrospinal fluid (CSF) in tuberculous meningitis, pleural fluid and biopsy for pleural disease, as well as bone marrow and liver biopsy in disseminated tuberculosis.

1.1.7 Treatment

1.1.7(a) Aims

The aims of treatment of tuberculosis include to reduce morbidity resulted from tuberculosis infection, to prevent mortality caused by tuberculosis, to prevent relapse of tuberculosis, to decrease transmission of tuberculosis to other people and to prevent the emergence of multidrug-resistant tuberculosis (Ministry of Health Malaysia, 2002).

1.1.7(b) Chemotherapy

Five drugs are considered essential (first-line) for the treatment of tuberculosis. These are isoniazid (H), rifampicin (R), pyrazinamide (Z), streptomycin (S) and ethambutol (E) (Ministry of Health Malaysia, 2002). More recently, streptomycin has been included as a second-line drug. Other second-line drugs include kanamycin, amikacin, capreomycin, ethionamide, cycloserine, p-Aminosalicylic acid (PAS), and fluoroquinolones such as ofloxacin, levofloxacin, gatifloxacin and moxifloxacin (Kasper DL *et al*, 2005).

1.1.7(b)(i) Isoniazid

Isoniazid is a first-line agent for treatment for all forms of tuberculosis caused by organisms known or presumed to be susceptible to the drug. It has profound early bactericidal activity against rapidly dividing cells (Hafner R *et al*, 1997).

The recommended dosage of isoniazid is 5-8 mg/kg for daily dosage, and 15-20 mg/kg for biweekly dosage.

1.1.7(b)(ii) Rifampicin

Rifampicin, also a first-line antituberculosis drug, has activity against organism that are dividing rapidly (early bactericidal activity) and against semidormant bacterial populations, thus accounting for its sterilizing activity (Dickinson JM & Mitchison DA, 1981). It is an essential component of all short-course regimens.

The recommended dosage of rifampicin is 10-15 mg/kg for daily dosage, and 15-20 mg/kg for biweekly dosage.

1.1.7(b)(iii) Pyrazinamide

Pyrazinamide, another first-line antituberculosis drug, exert greatest activity against the population of dormant or semidormant organisms contained within macrophages or the acidic environment of caseous foci (Girling DJ, 1984).

The recommended daily dosage of pyrazinamide is 20-40 mg/kg.

1.1.7(b)(iv) Streptomycin

Streptomycin and ethambutol have been shown to be approximately equivalent when used in the initial phase of treatment with 6-month regimens. However, among patients likely to have acquired *M. tuberculosis* in a high-incidence country, it has relatively high rate of resistance.

The recommended dosage of streptomycin is 15-20 mg/kg for daily dosage, and 15-20 mg/kg for biweekly dosage.

1.1.7(b)(v) Ethambutol

Ethambutol is included in the initial treatment regimens primarily to prevent emergence of rifampicin resistance when primary resistance to isoniazid may be present (Blumberg HM *et al*, 2003).

The recommended daily dosage of ethambutol is 15-25 mg/kg.

1.1.7(c) Treatment Regimens

Treatment regimens are divided into initial (or intensive) phase and continuation (or maintenance) phase (Ministry of Health Malaysia, 2002).

1.1.7(c)(i) Intensive Phase

During the intensive phase, three or four drugs are given daily. During this phase, the majority of the tubercle bacilli are killed, symptoms resolve and the patient becomes non-infectious (Kasper DL *et al*, 2005). This leads to rapid sputum conversion and amelioration of clinical symptoms.

This phase requires two months of daily doses of antituberculosis drugs. Recommended regimens include 2SHRZ (daily streptomycin, isoniazid, rifampicin and pyrazinamide for two months), 2EHRZ (daily ethambutol, isoniazid, rifampicin and pyrazinamide for two months) and 2HRZ (daily isoniazid, rifampicin and pyrazinamide for two months) (Ministry of Health Malaysia, 2002).

1.1.7(c)(ii) Maintenance phase

During the maintenance phase, two or three drugs are usually given intermittently. This phase is required to eliminate persisting mycobacteria and prevent relapse (Kasper DL *et al*, 2005).

This phase requires at least another four months of intermittent antituberculosis medications, and may be extended for severe forms of extrapulmonary tuberculosis and immunocompromised patients.

The available regimens include $4H^2R^2$ (twice-weekly isoniazid and rifampicin for four months), $4S^2H^2R^2$ (twice-weekly streptomycin, isoniazid and rifampicin for four months), 4HR (daily isoniazid and rifampicin for four months), $4H^3R^3$ (thrice-weekly isoniazid and rifampicin for four months) and $4S^3H^3R^3$ (thrice-weekly streptomycin, isoniazid and rifampicin for four months) (Ministry of Health Malaysia, 2002).

1.1.8 Monitoring Response and Compliance

1.1.8(a) Treatment Response

In order to monitor sputum conversion and treatment outcome, it is recommended that all patients who are initially sputum smear-positive to repeat sputum smears examination at the end of the second month of treatment. Additional sputum smears are taken at the fourth month and at the end of the regimens (Ministry of Health Malaysia, 2002).

Patients who do not achieve sputum conversion by two months will require an extended treatment. Smear positives documented after five months are indicative of treatment failure (Kasper DL *et al*, 2005).

1.1.8(b) Patient's Compliance

Compliance is very important in the management of tuberculosis patients. Patient's non-compliance is the main cause of treatment failure as well as the emergence of multidrug-resistant tuberculosis. A very high treatment completion rate can be achieved by adequate patient education. Directly observed treatment, short-

course therapy (DOTS) has been shown to be feasible and highly successful towards achieving the objective of a 95 percent cure rate (Ministry of Health Malaysia, 2002).

1.1.9 Drug Toxicity

During treatment, patients should be monitored for drug adverse effects and toxicity, the most common being drug-induced hepatitis.

1.1.9(a) Antituberculosis Drugs and Adverse Effects

Antituberculosis drugs are known to have many adverse effects. Some are mild and transient; others are potentially hazardous and fatal.

1.1.9(a)(i) Isoniazid

The most important adverse effect of isoniazid is hepatotoxicity. This includes asymptomatic elevation of aminotransferases, clinical hepatitis and fatal hepatitis. These will be further discussed in the next section.

Approximately 20 percent of patients taken isoniazid develop anti-nuclear antibodies, in which less than one percent develop clinical lupus erythematosus that requires drug discontinuation. Other adverse effects include hypersensitivity reactions such as fever, rash, Stevens-Johnson syndrome, haemolytic anaemia and vasculitis which are rare (Blumberg HM *et al*, 2003).

Isoniazid may also cause peripheral neurotoxicity which is dose-related and is uncommon (less than 0.2%) at conventional doses (Ormerod LP & Horsfield N, 1996). The risk is increased in persons with other conditions that may be associated with

neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure and alcoholism. Pyridoxine supplementation is recommended to help prevent this neuropathy (Snider DE, 1980).

1.1.9(a)(ii) Rifampicin

Apart from hepatotoxicity, rifampicin may cause cutaneous reactions. Pruritis with or without rash may occur in as many as 6 percent of patients but is generally self-limited (Villarino ME *et al*, 1997).

Gastrointestinal reactions such as nausea, anorexia and abdominal pain are rarely severe enough to discontinue the drug (Villarino ME *et al*, 1997). Orange discolouration of bodily fluids (sputum, urine, sweat and tears) is a universal effect of the drug, and patients should be warned beforehand (Blumberg HM *et al*, 2003).

Severe immunologic reactions such as thrombocytopenia, haemolytic anaemia, acute renal failure, and thrombotic thrombocytopenic purpura may also occur rarely, in less than 0.1 percent of patients (Lee C-H & Lee C-J, 1989).

1.1.9(a)(iii) Pyrazinamide

Pyrazinamide may cause nausea and mild anorexia at standard dose (Blumberg HM *et al*, 2003). Polyarthralgias may occur in up to 40 percent of patients receiving daily doses of pyrazinamide, but rarely requires drug adjustment or discontinuation (Jenner PJ *et al*, 1981).

Asymptomatic hyperuricaemia is an expected effect of pyrazinamide and is generally without adverse consequences (Combs DL *et al*, 1990). Acute gout is rare except in patients with pre-existing gout, and generally a contraindication to the use of pyrazinamide (Blumberg HM *et al*, 2003).

An effect of hepatotoxicity is discussed in the following section.

1.1.9(a)(iv) Ethambutol

The most important adverse effect of ethambutol is retrobulbar neuritis. This is manifested by decreased visual acuity or decreased red-green colour discrimination that may affect one or both eyes. The effect is dose related, with minimal risk at daily dose of 15 mg/kg. The risk is higher at higher doses given daily (18% of patients receiving more than 30 mg/kg per day) and in patients with renal insufficiency (Blumberg HM *et al*, 2003).

Rarely ethambutol can cause peripheral neuritis (Tugwell P & James SL, 1972). Cutaneous reactions requiring discontinuation of the drug occur in 0.2-0.7 percent of patients (Doster B *et al*, 1973).

1.1.9(a)(v) Streptomycin

The most important adverse reaction caused by streptomycin is ototoxicity, including vestibular and hearing disturbances. The risk is increased with age and concomitant use of loop diuretics (Blumberg HM *et al*, 2003).

Nephrotoxicity can also occur but less compared to amikacin, kanamycin or capreomycin (Appel GB & Neu HC, 1977). Streptomycin, also relatively commonly causes circumoral parasthesias immediately after injection (Blumberg HM *et al*, 2003).

1.1.9(b) Monitoring of Drug Toxicity

Where facilities are available, all patients should have baseline measurements of liver enzymes, serum bilirubin, serum creatinine, blood urea and a full blood count. The purpose of these baseline tests is to detect any abnormality that would necessitate modification of the treatment regimen.

Patients with pre-existing liver disease or conditions such as alcoholism known to potentiate hepatotoxicity of antituberculosis drugs should have regular monitoring of liver function especially during the first few months of therapy.

All patients should be monitored clinically for adverse reactions during the period of chemotherapy. Routine laboratory monitoring for asymptomatic patients is not necessary. If symptoms suggesting drug toxicity occur, appropriate laboratory testing should be performed to confirm such toxicity (Ministry of Health Malaysia, 2002).

1.1.9(c) Management of Drug Toxicity

Minor side effects, such as gastrointestinal intolerance are best managed by reassurance and symptomatic treatment. The most common serious drug toxicity is hepatitis. Patients who develop symptoms of liver dysfunction such as nausea, vomiting, anorexia and abdominal pain during therapy should have their treatment stopped

immediately. Many of them may be successfully restarted on the same drugs, when liver functions return to normal (Ministry of Health Malaysia, 2002).

Patients who develop hypersensitivity reactions, such as rash, to the two most potent drugs i.e. isoniazid and rifampicin, may be desensitized later if a suitable regimen could not be provided with the other drugs which the patient can tolerate.

The development of a few conditions contraindicate the further use of the causative drug. These include thrombocytopenia, shock and/or renal failure due to rifampicin, visual impairment due to ethambutol and eighth cranial nerve damage from streptomycin (Ministry of Health Malaysia, 2002).

1.2 Drug-induced Liver Disease

1.2.1 Background

Hepatotoxicity is a potential complication of most prescribed drugs, presumably due to the central role of the liver in drug metabolism. In a few cases the adverse liver reactions are predictable and dose dependent; however for most drugs liver injury is idiosyncratic (Aithal PG & Day CP, 1999).

Therapeutic drugs remain a significant cause of liver injury and can be associated with a variety of histological appearances including chronic hepatitis. The pattern of drugs causing liver damage is changing and most often is due to a rare side effect of commonly prescribed drugs such as antibiotics and anti-inflammatory drugs, and to recently introduced drugs whose hepatotoxicity may not yet be established (Aithal PG & Day CP, 1999).

1.2.2 Incidence

Even though many drugs associated with a significant risk of hepatotoxicity have been replaced by apparently safer drugs, hepatic drug reactions are being increasingly reported, with drugs still accounting for five percent of cases of jaundice admitted to hospitals (Friis H & Andreasen PB, 1992).

Drug-induced hepatic injury is the most frequent reason cited for the withdrawal from the market of an approved drug, and it also accounts for more than 50 percent of the cases of acute liver failure in the United States (Lee WM, 2003).

1.2.3 Types of Drug Reactions

Most drugs cause liver injury infrequently. These reactions are considered idiosyncratic, occurring at therapeutic doses from 1 in every 1000 patients to 1 in every 100,000 patients, with a pattern that is consistent for each drug and for each drug class. Idiosyncratic reactions are characterized by a variable delay or latency period, ranging from 5 to 90 days from the initial ingestion of the drug, and are frequently fatal if the drug is continued once the reaction has begun (Lee WM, 2003).

In contrast, with a drug such as isoniazid, mild injury may disappear despite continued use. Others, such as acetaminophen, are dose-dependent hepatotoxic reactions (Lee WM, 2003).

Hepatoxic reactions are dependent on several parameters such as dosage of drug received, patient's age, sex, and body mass index which affect metabolism, as well as

concurrent use of certain foods and drugs, physiologic changes such as pregnancy, and underlying renal or liver disease.

For reasons that are unclear, women generally predominate among patients with drug-induced liver injury, as illustrated in a study in which women accounted for 79 percent of reactions due to acetaminophen and 73 percent of idiosyncratic drug reactions (Ostapowicz G *et al*, 2002).

1.2.4 Mechanisms

The features of idiosyncratic drug reactions: their rarity, their severity, and their resolution despite continued use of the drugs by patients with phenotypes that appear to be adaptive, might be explained by a series of events that first involve intracellular disruption, cell necrosis (or apoptosis), followed by activation of the immune sequence (Watkins PB, 1992).

Hepatotoxicity may wax and wane with continuing drug use, implying that suppressor or attenuator pathways are active (Watkins PB, 1992). Immune responses, once initiated, may be amplified or suppressed by means of the class I and class II major-histocompatibility-complex cell-surface receptors. Cell-surface neoantigens may be short-lived, but they reappear with continued exposure to the drug (Robin M-A *et al*, 1997).

1.2.5 Clinical Consequences

The most frequent hepatotoxic drug reactions evoke moderate-to-severe injury to hepatocytes with a clinical picture that resembles viral hepatitis, characterized by a rapid onset of malaise and jaundice in association with elevated aminotransferases

levels. Each drug has its own pattern of injury. If hepatocytes injury predominates, aminotransferase levels may be at least five times as high as normal. In cholestatic syndromes, elevations of alkaline phosphatase and bilirubin levels predominate. Acute liver failure may develop after a week or more of illness, particularly if the offending drug is continued (Lee WM, 2003).

1.2.5(a) Idiosyncratic Reactions

Idiosyncratic drug reactions made up 20 percent of cases of severe liver injury requiring hospitalization in a United States study involving 307 patients at six hospital centers (unpublished data). A variety of clinical patterns are observed such as hepatocellular with isoniazid, cholestasis with erythromycin and autoimmune reactions with lovastatin. The majority of idiosyncratic reactions involve damage to hepatocytes throughout the hepatic lobule, with various degrees of necrosis and apoptosis. Symptoms of hepatitis occur typically within days or weeks after the initial exposure and may continue to evolve even after the offending drug is withdrawn (Lee WM, 2003).

1.2.5(b) Allergic Reactions

Some drug reactions have a striking allergic component such as sulfa drugs which may induce fever, rash and eosinophilia, and phenytoin may result in fever, lymphadenopathy and rash. In most instances, it is slow to resolve that suggests that allergens remain on the hepatocytes surface for weeks or months. Rapid recognition of toxic effect and immediate discontinuation of the offending drug are important to limit hepatic and cutaneous damage (Lee WM, 2003).