REVIEW

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Tuberculosis Treatment in Patients with Comorbidities

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Tuberculosis is a significant infectious problem in elderly patients with comorbidities in Korea. The age-associated diseases such as malignancy and diabetes mellitus may increase the risk of tuberculosis in this population. The medication treatments of tuberculosis in patients with comorbidities can cause adverse reactions to antituberculosis drugs and inadequate treatment responses. Thus, clinicians must carefully monitor the toxicity of antituberculosis therapy and the efficacy of treatment in patients with comorbidities.

Keywords: Tuberculosis; Therapeutics; Comorbidity

Introduction

Tuberculosis is a significant infectious problem in elderly patients with comorbidities in Korea[1]. The incidence of tuberculosis is increasing in older patients, and some have multiple comorbidities. This review summarizes the treatment of tuberculosis in patients with comorbidities including hepatic disease, chronic kidney disease, solid-organ transplantation, and solid malignant disease. This review is based on the Korean Guidelines for Tuberculosis, first edition, 2011[2].

Hepatic Disease

Drug-induced liver injury (DILI) is a problem associated with the treatment of tuberculosis. Chronic liver disease is known to increase the risk of DILI. DILI in patients with advanced liver disease is potentially serious, even life-threatening[3]. Thus, clinicians must carefully monitor hepatic function in patients with liver disease during the treatment of tuberculosis. The choice of the treatment regimen used in the setting of liver disease depends on the severity of both the liver disease and the tuberculosis (Table 1)[2-4].

Lee et al.[5] reported that tuberculosis treatment in hepatitis B surface antigen (HBsAg)-positive inactive carriers can be performed in the usual manner, using standard short-course regimens of isoniazid, rifampin, ethambutol, and/or pyrazinamide with careful monthly monitoring of liver function. In that study, the authors showed that DILI occurred more frequently in HBsAg carriers (9 of 110 carriers, 8%) than in control subjects (4 of 97 controls, 4%). However, after the recovery of liver function, isoniazid and rifampin were successfully reintroduced as therapy. Park et al.[6] reported on the treatment of tuberculosis in patients with chronic hepatitis and cirrhosis. In that study, the authors showed that hepatotoxic antituberculosis drugs might be safely used in patients with chronic liver disease, including compensated cirrhosis, if the number of hepatotoxic drugs used was appropriately adjusted.

Renal Insufficiency and End-Stage Renal Disease

Renal insufficiency complicates the treatment of tuberculosis because some antituberculosis drugs are cleared by the

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Table 1. Possible regimen of antituberculosis treatment in patients with hepatic disease*

Underlying hepatic disease	Possible regimen	
Inactive HBsAg carrier Inactive HCV carrier Past history of acute hepatitis Alcohol drinker	Standard short-course regimen 1) 6HREZ/4HR(E) 2) 9HRE	Monitor liver function Stop drinking
Chronic liver disease with stable liver function	9HRE	Monitor liver function
Advanced liver disease Unstable liver function Hepatic encephalopathy	1) Two hepatotoxic drugs 9HRE 6-9 REZ 2HRES/6HR 2) One hepatotoxic drug 12-18 RE/FQ/CS/injectables 2HES/10HE 3) No hepatotoxic drugs 18-24 E/FQ/CS/injectables	Refer to experts

*Based on the Korean guidelines for tuberculosis, 1st edition (2011)[2], Treatment of tuberculosis guidelines, 4th edition (2010)[4], and American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis (2003)[3].
HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; H: isoniazid; R: rifampin; E: ethambutol; Z: pyrazinamide; S: streptomycin; FQ: fluoroquinolone; CS: cycloserine.

Table 2. Dosing recommendations for adult patients with reduced renal function and for adult patients undergoing hemodialysis*

Drug	Change in frequency	Recommended dose and frequency for patients with Ccr of <30 mL/min or patients undergoing hemodialysis
Isoniazid	No change	300 mg once daily
Rifampin	No change	600 mg once daily
Pyrazinamide	Yes	25–35 mg/kg three times per week
Ethambutol	Yes	15–25 mg/kg three times per week
Levofloxacin	Yes	750–1,000 mg three times per week
Moxifloxacin	No change	400 mg once daily
Cycloserine	Yes	250 mg once daily or 500 mg three times per week
Ethionamide	No change	250–500 mg once daily
p-Aminosalicylic acid	No change	4 g twice daily
Streptomycin	Yes	12–15 mg/kg two or three times per week
Capreomycin	Yes	12–15 mg/kg two or three times per week
Kanamycin	Yes	12–15 mg/kg two or three times per week
Amikacin	Yes	12–15 mg/kg two or three times per week

*Reprinted from Blumberg et al.[3] Am J Respir Crit Care Med 2003;167:603-62, with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society; reprinted from Joint Committee for the Development of Korean Guidelines for Tuberculosis, Korea Centers for Disease Control and Prevention[2].
Ccr: creatinine clearance.

kidney. Management may be further complicated by the removal of some antituberculosis drugs via hemodialysis[3]. Thus, clinicians should carefully monitor the potential development of drug-induced toxicity and the efficacy of antituberculosis treatment in patients with renal insufficiency. Some antituberculosis drugs require adjustment of their dosing and administration time intervals. Vitamin B6 should be given to these patients to prevent peripheral neuropathy due to isoniazid. The recommendations for adjustment of antituberculosis drug are shown in Table 2[2,3] and Table 3[7].

Table 3. Recommended dose of first-line drugs in patients with chronic kidney disease (CKD)*

	Stage 1–3 CKD†	Stage 4 and 5 CKD‡
Isoniazid	300 mg daily	300 mg daily
Rifampicin	<50 kg: 450 mg daily ≥50 kg: 600 mg daily	<50 kg: 450 mg daily ≥50 kg: 600 mg daily
Pyrazinamide	<50 kg: 1.5 g daily ≥50 kg: 2 g daily	25–30 mg/kg three times per week
Ethambutol	15 mg/kg daily	15–25 mg/kg three times per week (max 2.5 g)
Moxifloxacin	400 mg daily	Not suitable for three times weekly

*Reproduced from British Thoracic Society Standards of Care Committee and Joint Tuberculosis Committee et al.[7] Thorax 2010;65:557-70, with permission of BMJ Publishing Group Ltd. †Stage 1 CKD: normal creatinine clearance and function with urinary tract abnormality, Stage 2 CKD: creatinine clearance of 60–90 mL/min, Stage 3 CKD: creatinine clearance of 30–60 mL/min. ‡Stage 4 CKD: creatinine clearance of 15–30 mL/min, Stage 5 CKD: creatinine clearance of <15 mL/min with or without dialysis.

Solid-Organ Transplant

The risk for tuberculosis in patients with solid-organ transplantation is estimated to be 20 to 74 times greater than that in the general population[8]. Because of the challenge of treating active tuberculosis after transplantation, every effort must be made to diagnose and treat active tuberculosis before transplantation. The standard short-course treatment for active tuberculosis is recommended in patients undergoing transplantation[8]. The major difficulty in administering antituberculosis drugs to transplant patients is drug-drug interactions involving rifampin. Rifampin is a strong inducer of the microsomal enzymes that metabolize cyclosporine, tacrolimus, sirolimus, and corticosteroids. It may be difficult to maintain adequate levels of immunosuppressive drugs while using rifampin. Successful use of rifampin has been reported in transplant recipients, but the doses of cyclosporine, tacrolimus, and sirolimus must be increased at least two- to five-fold[8].

Solid-Organ Malignancy

There are no specific guidelines for the treatment of tuberculosis in patients with solid-organ malignancy. Standard treatment for tuberculosis is recommended in this population. Kim et al.[9] reported that the radiographic and clinical treatment responses during anticancer chemotherapy were not clinically different between tuberculosis-infected patients with (n=24) and without (n=48) solid-organ malignancy.

Conclusion

Tuberculosis is still a significant public health concern in Korea. The growing elderly population with higher incidences of comorbidities has a risk of developing tuberculosis. Clinicians must monitor the side effects of and response to antituberculosis therapy in patients with comorbidities.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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