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Treatment Management in Hepatitis and Tuberculosis Coexistence

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Abstract

Introduction: Tuberculosis (TB) is still a global problem. Drug resistance is caused by factors such as drug side effects, accompanying comorbidities and treatment compliance problems. Hepatitis infection has a high incidence in our country and presents with liver involvement and symptoms leading to cirrhosis. Therefore, if hepatitis infection accompanies TB patients, treatment management becomes difficult.The aim of this study is to draw attention to the cure rates in treatment with an appropriate treatment approach, despite the side effects, drug resistance and accompanying comorbidities that occur in the coexistence of TB and hepatitis.

Materials and Methods: 78 patients with Hepatitis A, B, C(HAV, HBV, HCV) coexistence with pulmonary tuberculosis between 2017-2019 were evaluated retrospectively. Demographic characteristics, hepatitis marker positivity, antiviral treatment, microbiological diagnosis, drug sensitivity test, drug side effects, treatment regimen and treatment results were evaluated retrospectively.

Results: The patients are 31% women; 45% HBV, 45% HCV, 10% HAV were detected. There are 76% Acid Resistant Bacteria positive and 73% of them were sensitive to all drugs. Diabetes, Chronic Obstructive Pulmonary Disease, substance abuse and psychological disorder were the most common comorbidities. 30% of the patients had high admission liver function tests and 27% received a non-hepatotoxic treatment regimen. The most common side effects were hepatotoxicity, hypersensitivity, ototoxicity, and neurological side effects. 61% of the patients were able to complete TB treatment in 6 months. Cure was observed in 72% of the patients.

Conclusion: Although disease management becomes difficult when TB and hepatitis coexist, cure rates increase with an appropriate treatment approach.

Key words: Hepatitis infection; hepatotoxicity; tuberculosis.

Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis complex bacilli. Despite advances in healthcare, TB is still one of the most important health problems in the world. It is one of the leading causes of deaths worldwide (1). A study conducted in Asia found that the epidemic is ageing and is more common in men. In some countries, tuberculosis control can be achieved more easily with existing strategies and technologies (2). There are studies arguing that lung x-ray interpretation with artificial intelligence can also be used in TB screening (3). In 2021, these trends are notable as World Health Organization (WHO) revised its TB screening guidelines, issuing guidance for the first time on the use of AI software as an alternative to human readers to interpret digital X-rays to screen individuals aged 15 years and older for TB (4). Timely diagnosis and initiation of treatment is the key to infection control. Vaccination, detection of infection, and provision of preventive treatment are key elements of tuberculosis prevention (5). If not treated appropriately and timely, recurrence, resistance and mortality rates increase. Isoniazid-Rifampicin-Pyrazinamide-Ethambutol (HRZE) is used in standard quadruple TB treatmen. When not treated appropriately and timely, relapse, resistance and mortality rates increase. Multidrug-resistant-TB (MDR-TB) strains have higher recurrence and mortality rates compared to susceptible strains. MDR-TB is also a risk factor in terms of the emergence of common drug resistant TB (XDR-TB) (6-8). Although tuberculosis exacerbates with the emergence of Human Immmunodeficiency Virus (HIV) infection in developing countries, this is not the case in our country. Infections caused by Hepatitis B and Hepatitis C virus, which are transmission routes similar to HIV, are a more serious danger to our country than Acquired Immune Deficiency Syndrome (AIDS). The number of HIV-carrier people worldwide is around 20-30 million, hepatitis B virus carrier 350 million and the number of people infected with hepatitis C virus is more than 300 million (9-11). That is why WHO aims to eliminate viral hepatitis as a health

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problem globally. WHO aimed for a 65% reduction in hepatitis-related deaths and a 90% reduction in new infections by 2030 (12). As TB can cause hepatitis, high liver function test (LFT) can cause; One of the most common side effects of anti-TB therapy is hepatotoxicity. LFT height will decrease with anti-TB treatment due to TB hepatitis. However, if there is hepatotoxicity due to anti-TB treatment, the treatment should be discontinued. Therefore, it should be distinguished well (13). In addition, if there is a hepatitis virus infection accompanying TB infection, treatment management becomes increasingly difficult. Treatment delay due to high LFT at admission and / or interaction between antiviral treatments and anti-TB treatment puts clinicians in a difficult position. In order to avoid delay in treatment, a non-hepatotoxic treatment regimen should be applied to those who cannot tolerate conventional TB treatment. In the treatment management of patients, the department of infection and chest diseases should work in coordination. In this study, it was aimed to investigate the treatment management and possible side effects of inpatient TB with Hepatitis A, Hepatitis B or Hepatitis C infection.

Materials and Methods

In the study, the patients hospitalized with a diagnosis of tuberculosis and accompanied hepatitis A, B, C (HAV, HBV, HCV) between 01.01.2017 and 31.12.2019 were included. Treatment regimen and treatment results of 78 patients with HAV, HBV, HCV coexistence with pulmonary tuberculosis hospitalized were evaluated retrospectively. Demographic characteristics, nationality, and additional diseases of the patients were recorded. Hepatitis marker positivity, hepatitis carrier and active status, antiviral treatment used, microbiological diagnosis and follow-up, sputum conversion and culture conversion time, drug sensitivity test, laboratory values (Aspartate Transaminase 'U/L'), Alanine Transaminase 'U/L', Bilirubin), the treatment regimens taken by the patients, drug side effects, treatment regimen changes due to drug side effects and their results were evaluated retrospectively. Hepatitis screening (HBsAg, AntiHBs, Anti-HCV, Anti-HAV) is routinely performed for patients hospitalized with a diagnosis of tuberculosis. In case of hepatitis antigen and/or antibody positivity, according to the infectious diseases consultation, DNA and/or RNA is requested if necessary. Hepatitis antigen / antibody and DNA / RNA profiles of the patients and their carrier or active hepatitis status were determined. The treatment regimen was arranged in consideration of the Tuberculosis Diagnosis and Treatment Guidelines. In case of hepatotoxicity, drug desensitization was performed and an appropriate treatment regimen was arranged. A non-hepatotoxic treatment regimen was used for patients with active Hepatitis A, B, and C disease (13). Inclusion criteria in the study; Patients aged 18 years or older, with a diagnosis of hepatitis A/B/C carrier or active (hepatitis antigen/antibody, DNA/RNA positivity or cytology diagnosis), bacteriological and/or clinical radiological diagnosis of pulmonary tuberculosis were determined. The exclusion criteria with an uncertain diagnosis of hepatitis, and patients without a diagnosis of bacteriological and/or clinical radiological pulmonary tuberculosis. Searching for Acid Resistant Bacteria (ARB) with microscopic examination in the diagnosis of TB, although fast and cheap, has low sensitivity. Culture is the gold standard in diagnosis, and drug susceptibility testing (IDT) is performed with culture methods (7-9). Sputum ARB was requested from the patients three times at the time of diagnosis and one at the monthly controls. Culture was studied from each sputum sample. IDT was performed at the beginning of treatment and in the third month. The controls of the patients were made with monthly sputum harb, culture, biochemistry, hemogram, and x-ray. The patients were classified according to their case definitions. The new case includes patients who have not received TB treatment before or who have received treatment for less than a month; The previously treated case includes cases that have relapsed, returning out of follow-up, and treatment failure (13). Hepatotoxicity; It is the transaminase values exceeding 5 times the normal regardless of the symptom, 3 times the transaminase values in the patient with hepatitis symptoms or the bilirubin value exceeding 1.5 mg/dl. Non-hepatotoxic regimen Ethambutol, streptomycin, moxifloxacin, cycloserine (high-dose pyridoxine with cycloserine) is started. It is trying to add rifampicin gradually and then isoniazid. Treatment results; treatment success (cure and treatment completion), treatment failure, out of follow-up, transplant, ongoing treatment, and death (13).

Ethical approval and informed consent: Ethics committee approval no. 2018 14/118 was obtained from the institution where the study was conducted. It was included an Informed consent statement, a Declaration of Helsinki statement, and ethical approval from an ethics committee.

Table 1: Diagnosis, treatment and demographic characteristics with all of hepatitis and tuberculosis

Variables	n (%)
Sex	
Female	24 (30.8)
Male	54 (69.2)
Diagnosis method	
Sputum smear ARB +	59 (75.6)
TB Culture +	10 (12.8)
Histopathological	4 (5.1)
Clinical-radiological	5 (6.4)
Drug Sensitivity	
HRZE sensitive	57 (73.1)
Rifampicin resistance (RR)	6 (7.6)
Multidrug resistance (MDR)	5 (6.4)
Pre-diffuse drug resistance (Pre-XDR)	6 (7.6)
Common drug resistance (XDR)	4 (5.1)
Comormidity	
DM	11 (14.1)
COPD	8 (10.3)
Substance Abuse	5 (6.4)
Psychological Disorder	3 (3.9)
HT	6 (7.7)
Treatment	
HRZE	57 (73.1)
Non-hepatotoxic regimen	21 (26.9)
Side effects	
Hepatotoxicity	7 (9.0)
Hypersensitivity	8 (10.3)
Ototoxicity	3 (3.9)
Neurological	4 (5.1)
Defect of vision	1 (1.3)
Acute renal failure	1 (1.3)
Second side effects	8 (10.3)
Treatment outcome	
Cure with 6 month therapy	48 (61.5)
Treated longer than 6 months	24 (30.8)
Death	3 (3.8)
Treatment failure	3 (3.8)

ARB; Acid Resistant Bacteria, **COPD;** Chronic Obstructive Pulmonary Disease, **DM;** Diabetes, **HT;** Hypertension **HRZE;** Isoniazid-Rifampicin-Pyrazinamide-Ethambutol, **TB;** Tuberculosis

Results

24 of 78 patients included in the study were women; 35 HBV, 35 HCV, 8 HAV were detected. In addition, 5 patients were accompanied by HIV. 59 of the patients were smear positive and 57 were sensitive to all drugs. Among the comorbidities, diabetes was associated with 11, COPD 8, substance abuse in 5 patients (Table 1). It consisted of 66 new cases, 6 relapses, 3 returning from treatment failures. In 23 of the patients, admission was high LFT. HRZE was applied to 57 patients and non-hepatotoxic regimen (moxifloxacin, cycloserine, streptomycin, ethambutol) was applied to 21 patients. 2 patients had high LFT at admission, but HRZE treatment was applied by drug desensitization. Resistant tuberculosis treatment was applied to 21 patients (Table 1). Of the 24 patients with side effects, 7 had hepatotoxicity, 8 had hypersensitivity, 4 had neurological side effects, 3 had ototoxicity (Figure 1). Second side effect occurred in 8 patients.

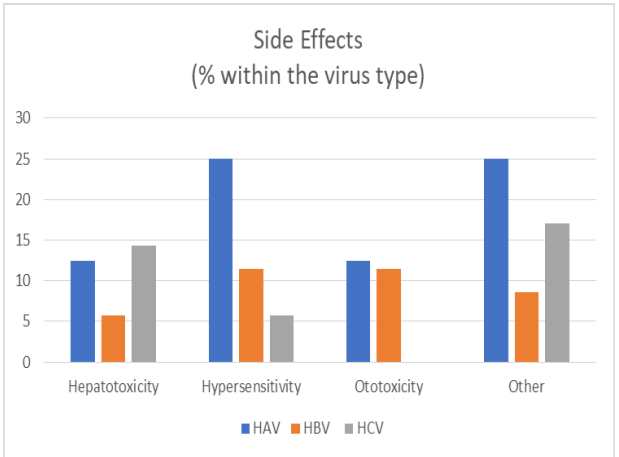

Figure 1. Treatment side effects of cases according to hepatitis virus types

Table 2: Demographic characteristics and treatments among hepatitis groups

	HAV n (%)	HBV n (%)	HCV n (%)	p
Male	6 (75)	23 (66)	24 (71)	0.8
Diagnosed with smear pozitive	7 (88)	24 (67)	28 (80)	0.6
HRZE sensitive	6 (75)	30 (86)	23 (66)	0.14
Treatment HRZE	7 (88)	28 (80)	22 (63)	0.16
Side effects pozitive	5 (63)	9 (26)	10 (29)	0.11
Cure treatment in 6 months	3 (43)	23 (66)	22 (63)	0.5

HAV; HBV; HCV: Hepatit **A; B; C, HRZE;** Isoniazid-Rifampicin-Pyrazinamide-Ethambutol

Secondary side effect; There were 2 ototoxicity, 2 neurological side effects, 1 hepatotoxicity, 1 thrombocytopenia, 1 visual impairment, 1 hypersensitivity reaction. There were no significant differences in demographic characteristics and treatments within the groups of hepatitis viruses (Table 2). While 67 of the patients started maintenance treatment in the 2nd month, TB treatment was completed in 6 months in 48 patients. There were 72 patients with cure, 3 deaths, and 3 treatment failures (Table 1).

Discussion

According to the World Health Organization (WHO) data, it reported tuberculosis (TB) in 8 million people in 1990. It was recorded that 2.9 million of them died and the majority of those who died were HIV (+) tuberculosis cases in Africa and Asia. Increasing association of tuberculosis has been found in AIDS patients (14). In our country, since the incidence of HIV infection is low, the association of tuberculosis is not as high as in the WHO data. On the contrary, hepatitis infection rates are higher in our country. Altindis et al. Although no association of HIV and tuberculosis was found in the study performed in patients, HBV and HCV infection and/or contact with TB were observed at high rates (11). Although hepatitis A (HAV) infection is generally a self-limiting infection, WHO reported that 7134 people died from HAV worldwide in 2016 (15). In our country, unlike HIV infection, attention should be drawn to hepatitis infection in terms of its frequency, and importance should be given to preventive measures, comorbidities, and timely treatment. Therefore, the risks that will increase in the presence of hepatitis and TB should be determined. In our study, hepatitis and TB coexistence were frequently detected. One third of the patients had high LFTs at admission. When hepatitis accompanies, treatment delay due to high LFTs increases the risk of transmission and drug resistance. In patients whose LFTs cannot be controlled, non-hepatotoxic treatment should be started as soon as possible to avoid treatment delays. As in our study, cure rates in treatment will increase in this way. The evaluating the data regions in Turkey and 9179 the total number of patients in the patients included in the study, the 15-24 and 25-34 age group than in the other age groups (11) and men in TB incidence rates were higher (12, 14, 16). In the study, association of tuberculosis was found more frequently in male patients in all hepatitis groups. Although TB notifications have improved over the years, there is no impact on the incidence rate due to undiagnosed and delayed diagnoses cases (17). According to statistics, in a total of 12046 patients diagnosed with TB in 2017, the new cases were 92.2% and the previously treated cases were 7.8% (13). Kocakoglu et al. The gold standard in TB diagnosis, the rate of diagnosis by culture was 0.8% of all smear positive and negative cases. In the presence of radiological and clinical findings, the rate of diagnosis with PPD positivity was 9.2% (18). Ozkara et al. In their study, the smear positivity rate was 70% in those who underwent sputum examination (15). In our study, although hepatitis was associated with TB patients, new cases (85%) and the number of smear positive cases were observed at similar rates (78%). There was no difference in the rates of smear positive cases between hepatitis A, B and C groups. There is an increasing pattern of resistance to antituberculosis drugs compared with previous studies. In some cases, drug resistance has been observed after antituberculosis treatment and in some cases from the beginning. Mutation and adaptation theory has been put forward in the formation of resistant strains. Adaptation theory is that after the administration of tuberculosis drugs, that drug becomes resistant over time. Therefore, physician and treatment follow-up is very important in TB treatment (19-21). No medication is added to any patient whose treatment fails or does not show improvement. While his treatment

is continued, he is refers to a center that provides resistant therapy. The institutions that should decide on the treatment of rifampicin resistance (RD)/MDR / XDR-TB patients in our country are chest diseases training and research hospitals (9). Tanriverdi et al. While 64 (82%) of 78 TB patients were susceptible to all antituberculosis drugs, resistance was found in 14 (18%) samples. While the number of MDR-TB was found to be 2 (2.5%), the number of cases resistant to all drugs was found to be 1 (1.2%) (22). Turkey in the years 2005-2018, according to statistics tuberculosis patients previously treated rates compared to new cases has declined in recent years. In our study, 57 patients (73%) sensitive to all drugs, 6 (8%) RIF resistance, 5 (6%) MDR, 6 (8%) Pre-XDR, and 4 (5%) patients were seen in the DRA. It was observed that the association of TB and hepatitis was more common with drug resistance in previously treated patients due to increased drug resistance. Despite the detection of drug resistance, maintenance treatment could be started in 86% of the patients in the 2nd month due to the presence of a center that can work on drug resistance and the initiation of appropriate treatment, and there was no need for treatment extension. The most common side effects in the studies were gastrointestinal and cutaneous side effects in the form of nausea and vomiting. Less frequent vestibular side effects and hepatitis have been seen. Side effects are usually seen in the first three months of treatment (13, 23, 24). Apart from hepatotoxicity, gastrointestinal side effects such as nausea and vomiting, skin reactions, peripheral neuropathy, atralgia, increased uric acid in the blood, flu-like picture associated with RIF, red / orange staining of body fluids and peroral drowsiness are called minor side effects (13, 25, 26). Hypersensitivity reactions, visual impairment, hepatotoxicity, hearing loss, hemolytic anemia, acute renal failure, shock, and thrombocytopenic purpura are major side effects (11). In our study, hepatotoxicity, hypersensitivity and neurological side effects were the most common side effects. Ototoxicity and neurological side effects were the most common secondary side effects during treatment follow-up. In drug-induced hepatotoxicity, the same drugs are restarted with the same doses when liver functions fall below normal values. A non-hepatotoxic treatment regimen is initiated in patients with drug-induced hepatotoxicity for the second time after hepatotoxicity. Although transaminases or bilirubin do not decrease within two weeks, a non-hepatotoxic treatment regimen is started. After the non-hepatotoxic treatment regimen, desensitization can be performed according to the transaminase values of the patient, and first RIF and then INH can be added (13). In 30% of the patients, admission was high LFT. Treatment was initiated by drug desensitization in patients other than active hepatitis according to the resistance pattern. Patients with active hepatitis were given a non-hepatotoxic treatment regimen. HRZE treatment was given to 73% of the patients. Although the admission LFT was higher in 2 patients, drug desensitization was performed and HRZE treatment was given. A non-hepatotoxic treatment regimen was applied to patients who LFT values increased again despite drug desensitization. When patients are accompanied by hepatitis infection, treatment delay due to hepatotoxicity causes drug resistance and treatment failure. Therefore, non-hepatotoxic treatment regimen should not be delayed in intolerant patients. As emphasized in the 2016 ATS guideline, there is resistance to treatment and treatment management becomes difficult in special conditions such as a history of accompanying liver and/or renal disease, HIV infection, extrapulmonary tuberculosis, culture-negative pulmonary tuberculosis, pediatric and pregnancy tuberculosis (27). Migrations, insufficiencies in the infrastructure system related to public health, HIV epidemic, inadequacy in patient follow-up and isolation procedures, delays in diagnosis and treatment, inadequacy of qualified personnel and the development of resistance to anti-tuberculosis drugs can be listed as the reasons for not preventing tuberculosis disease (28). HIV infection also increases the percentage of tuberculosis and extrapulmonary tuberculosis. In a study conducted in Spain, no cases of lymphadenitis tuberculosis were found in 65 new HIV (-) tuberculosis cases, while HIV (+) lymphadenitis tuberculosis was found in 25 (39%) of 65 new tuberculosis cases (29). Since HIV infection is less than the rate of hepatitis infection in our country, HIV was detected in only 5 patients and extrapulmonary tuberculosis was not accompanied. 81.7% of 650 TB cases in Erzurum between 2012-2018 did not have any additional disease. Diabetes mellitus (4.2%) and hypertension (3.7%) were common in patients with comorbid diseases. 92.9% of the cases resulted in completing the treatment, and HRZE was used most frequently in the treatment. In 43.1% of the cases treated, it was used in double combination for two months, four or four months (30). The most common comorbidities in our study were diabetes, chronic obstructive pulmonary disease and substance abuse. Maintenance treatment was

started in the second month in 86% of the patients. Cure was observed in 92% of the cases, death in 4%, and treatment failure in 4%. Although TB patients were accompanied by hepatitis, the success of treatment was observed at similar rates with appropriate anti-TB treatment. HBV infection was higher in cases that resulted in death.

Limitation of study: This review has several limitations. At the beginning, it was a retrospective study and studies with larger numbers of patients are needed.

Conclusion

Although attention is drawn to the association of HIV and tuberculosis all over the world, the rate of hepatitis carriage or chronic hepatitis in our country is higher than expected. In patients with low hepatic reserve, side effects and drug resistance are frequently detected, causing treatment delays and treatment failure. Non-hepatotoxic treatment regimen should be initiated without delay in patients who are intolerant by prioritizing patient-based therapy. As in our study, treatment completion and success rates increase with appropriate and timely treatment. More attention should be paid to the association of hepatitis and tuberculosis, as its incidence is high. Because it is a center that can provide resistant tuberculosis treatment, the incidence and case rates of various disease groups are increasing. However, being a retrospective study constitutes a limitation of the study.

Ethics committee approval: 2018 14/118 was obtained from the institution.

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