

Treatment and Management of Hypersensitivity Reactions Developed Against Anti-Tuberculosis Drug

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Abstract

Background: The World Health Organization Global Tuberculosis Report 2021 defines tuberculosis as the second infectious disease that causes sickness and death after COVID 19 and ranks it as the 13th among the global causes of death. However, the prevalence of the patients developing a hypersensitivity reaction against antituberculosis treatment is yet unknown. This study aimed to investigate the prevalence of drug allergy against antituberculosis treatment and the management of such a problem. **Methods:** This is a case—control study. All patients hospitalized in the tuberculosis inpatient service between February 01, 2015 and May 01, 2021 due to hypersensitivity reaction or who developed hypersensitivity during hospitalization were included in the case group. Patients who received inpatient treatment between the same dates and did not develop any drug allergy were included in the control group. The demographic characteristics of the patients, the tuberculosis diagnostic indicator, the type of hypersensitivity reaction that developed, the duration of the manifestation of the reaction and its treatment were evaluated for the purpose of the study. **Results:** A total of 2677 patients were hospitalized in the tuberculosis inpatient service between the specified dates. Two hundred and ten patients were consulted for drug hypersensitivity reactions in the Allergy Clinic. The prevalence of drug allergy in inpatients was calculated as 7.8%. One hundred and forty-eight patients examined by the authors were included in the study. Seventy-nine of the 148 patients (53.4%) who developed a hypersensitivity reaction were male, the mean age of these patients was 47.20 ± 18.95 years, 89.2% ($n = 132$) were citizens of the Republic of Turkey, 7.4% ($n = 11$) of the patients had received tuberculosis treatment before, 16.9% (25) had developed antituberculosis drug resistance and the bacteriological diagnosis was present in 79.7% (118) of the patients. Chi-square test results applied in the allergy group revealed that the risk of developing a hypersensitivity reaction is statistically significantly higher in female patients ($P < 0.001$), Turkish citizen patients ($P = 0.004$), in new cases ($P = 0.017$), in the group not diagnosed bacteriologically (histopathologically, clinically, and radiologically) ($P = 0.006$). The results of the logistic regression analysis performed also revealed that the risk of developing a hypersensitivity reaction is statistically significantly higher in female patients ($P = 0.006$), Turkish citizen patients ($P = 0.023$), in new cases ($P = 0.017$) and in the group not diagnosed bacteriologically (histopathologically, clinically, and radiologically) ($P = 0.006$). The success of the treatment was higher in the group that developed a hypersensitivity reaction compared to the control group. About 63.5% (94) of the patients examined developed Type I hypersensitivity reactions, whereas 36.7% (53) of the patients examined developed Type IV hypersensitivity reactions. Type I and Type IV reactions were observed simultaneously in a single patient. Considering the prevalence of developing a hypersensitivity reaction, pyrazinamide was determined as the drug inducing the hypersensitivity reaction in 25 (48.1%) patients. This figure was 15 patients (28.2%) for rifampicin, nine patients (17.3%) for isoniazid, and five patients (9.6%) for ethambutol. As a result, even patients who developed Type I or Type IV reactions were able to complete their antituberculous drug regimens with successful desensitization. **Conclusion:** The risk of developing an allergic reaction in patients who are administered on antituberculosis treatment is common, particularly in the first 2 months of treatment. However, we believe that the compliance of the patients to the antituberculosis treatment has been improved at the end of appropriate management of hypersensitivity reactions and the treatment results in success.

Keywords: Drug hypersensitivity, pyrazinamide, tuberculosis, type 1 hypersensitivity, type 4 hypersensitivity

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INTRODUCTION

The World Health Organization Global Tuberculosis Report 2021 defines tuberculosis as the second infectious disease that causes sickness and death after COVID 19 and ranks it as the 13th among the global causes of death.^[1] Tuberculosis is caused by *Mycobacterium tuberculosis* complex bacilli and is spread from person to person through the air.^[2,3] Early diagnosis and treatment reduce the risk of transmission. The risk of transmission and resistance will also increase if the patient fails to continue drug therapy for any reason whatsoever.^[3] The patient's antituberculosis drug treatment should be interrupted when the patient develops any hypersensitivity reaction against any of the drugs used. This situation not only delays the treatment but also causes an increase in the risk of transmission. Adverse effects of the medication that are not properly managed will also disrupt the patient's compliance with treatment. Proper management of the adverse effects of the medication will increase the success of treatment. It is necessary to plan a curative and preventive treatment regimen without deteriorating the patient's status. It is necessary to interrupt any treatment on the manifestation of hypersensitivity reactions; successful treatment may be further achieved by reintroducing appropriate drugs. Studies evaluating the hypersensitivity reactions developed by patients receiving antituberculosis therapy are often retrospective.^[4] In various epidemiological studies examining the incidence and prevalence of drug hypersensitivity reactions (DHRs) developed by tuberculosis patients, dermal reactions were noted as rash and exanthema, this is known to be an obstacle before defining the true prevalence.^[5] Data on the prevalence of DHRs associated with antituberculosis therapy in HIV-positive patients are available.^[4,6-8] However, there is no standard guideline recommendation for the hypersensitivity reactions developed due to antituberculosis drugs.

This study aimed to investigate the prevalence of drug allergy against antituberculosis treatment and the management of such a problem.

METHODS

Drug-susceptible adverse reactions include allergic, pharmacological, or pseudo-allergic states that develop through immunological or inflammatory mechanisms against the drug. Drug-susceptible adverse reactions are classified into two groups: Type A and Type B. Type A reactions account for 85%–90% of all drug-susceptible adverse reactions. These are referred to as the expected adverse effects after exposure to the drug. Type B reactions represent drug-susceptible hypersensitivity. Pursuant to Gell and Coombs's classification, DHRs that manifest through an immunological mechanism are examined in four groups.^[9-11] Recommendations of EAACI DHRs Guidelines and DHRs, published in 2019: Assessed and grouped as defined in the National Guidelines Update. Type I refers to the reactions mediated by immunoglobulin E (IgE) antibodies, whereas Type IV refers to the delayed reactions

mediated by T-cells. Type I IgE-mediated reactions clinically manifest with rash, itching, rhinitis, asthmatic complaints, urticaria, angioedema, and anaphylaxis. On the other hand Type IV reactions clinically manifest with reactions such as maculopapular eruption, acute generalized exanthematous pustulosis (AGEP), Stevens–Johnson Syndrome, toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms syndrome.^[9] Reactions that develop within the 1st h after taking the last dose of the drug are referred to as early-type reactions, reactions that develop between 1 and 6 h are referred to as “delayed early-type” reactions, those that develop between 6 and 12 h are referred to as the “accelerated delayed type” and those that develop after 12 h are referred to as delayed type reactions.^[10]

The study was designed as a retrospective case control. Our hospital, where we also have a Department of Allergy-Immunology, is the largest of the four reference hospitals to which resistant and challenging tuberculosis cases are referred. Case group comprised patients hospitalized in the tuberculosis inpatient service, patients who had developed a hypersensitivity reaction during their inpatient treatment and patients who consulted to the Allergy and Immunology clinic due to antituberculosis DHRs, between February 1, 2015 and May 1, 2021 and who were examined by the authors of this article. Patients who were hospitalized throughout the specified dates and had not developed any drug hypersensitivity were also included in the control group. All patients aged 18 years and older, who had developed drug-susceptible hypersensitivity while receiving antituberculosis treatment, were included in the study within the framework of the inclusion criteria. Patients with missing data in their files and patients with a micro bacterial infection other than tuberculosis were not included in the study. The primary aim of this study was to determine the prevalence of hypersensitivity reaction due to tuberculosis treatment and the secondary aim was to determine the success of the treatment applied in antituberculosis drug hypersensitivity.

Accordingly, the demographic characteristics of the patients, the tuberculosis diagnostic indicator, the type of hypersensitivity reaction that developed, the duration of the manifestation of the reaction and its treatment were evaluated. Tuberculosis diagnosis indicators were classified as smear positive, culture positive, molecular test positive, histopathological diagnosis, and clinical radiological diagnosis as determined in the Tuberculosis Diagnosis and Treatment Guide published by the Republic of Turkey Ministry of Health in 2020. The treatment plans of the patients were designated in accordance with the National Guidelines. Organ involvements were grouped as pulmonary and extrapulmonary and extrapulmonary sites of infection were further grouped as miliary, lymph node, pleura, kidneys, pericardium, and larynx. Previous treatment status of the patients was examined and the patients were reclassified as new cases and previously treated patients. Previously treated patients were also grouped as relapsed, returning patients due to nonfollow-up, and unsuccessful treatment. Patients were

divided into drug-resistant and drug-sensitive. Drug-resistant patients were also divided into 4 groups. (Isoniazid resistant, Rifampicin resistant (RR)/ Multidrug resistant (MDR) , Pre-Extensively Drug Resistant and Extensively Drug Resistant (EDR) tuberculosis).

Diagnostic tests

In case any hypersensitivity to any antituberculosis drug develops, all drugs should be discontinued. The type of reaction is essential for diagnostic tests. Our approach is to perform a skin prick testing for all drugs used in the patient's treatment. If available, prick and intradermal tests should be performed with parenteral forms; if not available prick test should be applied with tablets. Intradermal test, delayed reading, and patch tests are used in the diagnosis of T-mediated delayed reactions.

Desensitization

Desensitization is the administration of a drug by starting with much lower doses than the targeted dose and gradually increasing the dose at 30-min intervals allowing to develop a clinical tolerance without developing any hypersensitivity reaction.^[11-13] The Approach suggested by DHRs, published in 2019: Desensitization is defined in the Updated National Guidelines as the protocol developed for therapeutic purposes to safely administer a drug to which the patient has a proven or highly suspected hypersensitivity reactions.^[11] This tolerance continues as long as the drug continues to be administered. Although desensitization is actually recommended for Type I IgE-mediated reactions, it is also applied in clinical practice for reactions such as maculopapular eruption and fixed drug eruption, which are mild Type IV reactions.^[12,13]

During the desensitization application, the drug was administered in at least 6 steps where the drug dosage did not exceed 2.5 times and the drug administration time did not exceed 30 min. The drugs were administered under the supervision of a physician and nurse. For patients who have developed a Type I hypersensitivity reaction the process was as follows: each drug was administered via the desensitization method, if an allergic reaction did not develop, the next morning the drug was administered in full dose, and subsequently the new drug was administered by desensitization. In case any reaction developed, the patient was treated in accordance with international guidelines and the process was resumed after the treatment. After the regimen was completed, the patient was administered the full dose of the regimen for several days in one batch in the morning. The patient was discharged after it was observed that he could tolerate the drug without any problems. For patients who have developed a Type IV hypersensitivity reaction, the drug was administered by rapid desensitization. If an allergic reaction did not develop, only the drug administered through desensitization was given for 3 days, afterward a new drug was introduced. For patients who developed Type I or Type IV reactions, drugs were administered as isoniazid, ethambutol, rifampicin, and finally streptomycin/pyrazinamide, respectively. If secondary drugs are to be administered, drugs containing isoniazid, ethambutol, rifampicin, and streptomycin/

pyrazinamide were primarily administered. Afterward, other secondary drugs were given in no standard order.

All statistical analyzes of the study were performed using SPSS 22.0. (IBM Corp., Armonk, NY, USA). Differences in means were evaluated with the Mann–Whitney *U*-test. Relative risk, odd ratios and 95% confidence intervals were calculated. Chi-square and logistic regression analysis were used for categorical parameters.

This study was ethically approved by the ethics committee of the University of Health Sciences (dated June 03, 2021, protocol code: 116.2017. R-225)

RESULTS

Throughout the 75-month period between February 01, 2015 and May 01, 2021, 2677 patients received inpatient antituberculosis treatment in the tuberculosis clinic and 210 patients were consulted to the Allergy and Immunology Clinic of the hospital where the authors were assigned due to DHRs. The prevalence of DHRs in inpatients was calculated as 7.8%. One hundred and forty-eight patients examined by the authors were included in the study. Seventy-nine of 148 patients (53.4%) who developed a hypersensitivity reaction were male. Two hundred and six of the patients (72%) in the control group were male. The mean age (mean $\pm$ standard deviation [SD]) of the case group was calculated as 47.20 ± 18.95 . 89.2% (132) of the patients in the case group and 78% (223) of the patients in the control group were citizens of the Republic of Turkey. 7.4% ($n = 11$) of the patients in the case group had received antituberculosis treatment before, 16.9% (25) patients had developed antituberculosis drug resistance and bacteriological diagnosis was present in 79.7% (118) of the patients. According to the WHO tuberculosis report, tuberculosis cases are grouped and evaluated in six continents as Africa, America, Eastern Mediterranean, Europe, Asia, and Western Pacific. Of the patient group that developed a hypersensitivity reaction, 98% ($n = 145$) lived in the Asian continent and 2% ($n = 3$) lived in the European continent. Chi-square test results applied in the allergy group revealed that the risk of developing a hypersensitivity reaction is statistically significantly higher in female patients ($P < 0.001$), Turkish citizen patients ($P = 0.004$), in new cases ($P = 0.017$), in the group not diagnosed bacteriologically (histopathologically, clinically, and radiologically) ($P = 0.006$). The results of the logistic regression analysis performed in the allergy group also revealed that the risk of developing a hypersensitivity reaction is statistically significantly higher in female patients ($P = 0.006$), Turkish citizen patients ($P = 0.023$), in new cases ($P = 0.017$) and in the group not diagnosed bacteriologically (histopathologically, clinically, and radiologically) ($P = 0.006$). The success of the treatment was higher in the group that developed a hypersensitivity reaction compared to the control group [Table 1].

63.5% (94) of the patients examined developed Type I hypersensitivity reactions, while 36.7% (53) of the patients

Table 1: Demographic and clinic characteristics of allergy and control group

Variable	Total (%)	Allergy (%)	Control (%)	χ^2	Logistic regression	
Gender						
Male	285 (65.7)	79 (53.4)	206 (72)	<0.001	1	0.006
Female	149 (34.3)	69 (46.6)	80 (28)		2.358 (1.513-3.674)	
Nationality						
Foreign Country	79 (18.2)	16 (10.8)	63 (22)	0.004	1	0.023
TR	355 (81.8)	132 (89.2)	223 (78)		2.118 (1.109-4.046)	
Prior treatment						
Yes	57 (13.1)	11 (7.4)	46 (16.1)	0.017	1	0.017
No	377 (86.9)	137 (92.6)	240 (83.9)		2.419 (1.170-5.001)	
Diagnosis						
Bacteriology	375 (86.4)	118 (79.7)	257 (89.9)	0.006	1	0.006
Other (histopatology + clinical)	59 (13.6)	30 (20.3)	29 (10.1)		2.365 (1.280-4.371)	
Age						
18-35	147 (33.9)	37 (25)	110 (38.5)	0.054	1	0.895
36-50	99 (22.8)	37 (25)	62 (21.7)		1.075 (0.370-3.125)	
51-65	101 (23.3)	42 (28.4)	59 (20.6)		0.611 (0.210-1.784)	
66-80	66 (15.2)	26 (17.6)	40 (14)		0.454 (0.156-1.319)	
81-95	21 (4.8)	6 (4.1)	15 (5.2)		0.545 (0.181-1.646)	
Drug resistance						
Sensitive	354 (81.6)	123 (83.1)	231 (80.8)	0.551	1	0.367
Resistant	80 (18.4)	25 (16.9)	55 (19.2)		0.765 (0.428-1.367)	
Treatment duration						
Treatment success	320 (73.7)	114 (77)	206 (72)	0.009		
Treatment failure	6 (1.4)	1 (0.7)	5 (1.7)			
Nonfollow-up	15 (3.5)	3 (2)	12 (4.2)			
Dead	35 (8.1)	4 (2.7)	31 (10.8)			
Still under treatment	47 (10.8)	23 (15.5)	24 (8.4)			
Travel abroad for transplantation	11 (2.5)	3 (2)	8 (2.8)			

examined developed Type IV hypersensitivity reactions. Type I and Type IV reactions were observed simultaneously in a single patient. The most common Type I hypersensitivity reaction was urticaria with 38.5%, (57) and the most common Type IV hypersensitivity reaction was maculopapular eruption with 24.3%(36) [Table 2].

The drug responsible for inducing the hypersensitivity could be identified in 52 patients (35.2%). Considering the first-generation antituberculosis drugs administered in these 52 cases, pyrazinamide was determined as the drug inducing the hypersensitivity reaction in 25 (48.1%) patients. This figure was 15 patients (28.2%) for rifampicin, nine patients (17.3%) for isoniazid and five patients (9.6%) for ethambutol. Considering the second-generation antituberculosis drugs, moxifloxacin and PAS were determined as the drug inducing the hypersensitivity reaction in 3 (5.8%) patients. This figure was 2 (3.8%) for amikacin and prothionamide and 1 (1.9%) for linezolid. While a single drug was responsible for the reaction in 41 patients, multi-drug allergy was considered in 11 patients. Pyrazinamide was observed to be the most frequently responsible agent for Type I hypersensitivity reactions, whereas rifampicin was the most frequently responsible agent for developing Type IV hypersensitivity reactions [Table 3].

Table 2: Type of hypersensitivity reaction

Type of hypersensitivity reaction	Female, n (%)	Male, n (%)	Total, n (%)
Type I			
Pruritus	10 (6.8)	14 (9.5)	24 (16.2)
Urticaria	32 (21.6)	25 (16.9)	57 (38.5)
Angioedema	4 (2.7)	4 (2.7)	8 (5.4)
Urticaria+Angioedema	3 (2)	2 (1.4)	5 (3.4)
Type IV			
MPE	14 (9.5)	22 (14.9)	36 (24.3)
AGEP	-	-	-
Eritema multiforme	1 (0.7)	1 (0.7)	2 (1.4)
Lichenoid drug eruption	4 (2.7)	6 (4.1)	10 (6.8)
Fixed drug eruption	-	2 (1.4)	2 (1.4)
TEN	-	-	-
SJS	-	-	-
DRESS	1 (0.7)	1 (0.7)	2 (1.4)
Exfoliative dermatitis	-	1 (0.7)	1 (0.7)
Type I+IV			
Urticaria + MPE	-	1 (0.7)	1 (0.7)
Total	69 (46.7)	79 (53.3)	148 (100)

AGEP: Acute Generalized Exanthematous Pustulosis, DRESS: Drug Rash with Eosinophilia and Systemic Symptoms, SJS: Stevens-Johnson Syndrome, TEN: Toxic Epidermal Necrolysis, MPE: Maculopapular eruption

DHR developed in all patients (mean $\pm$ SD) at 16.41 ± 29.24 days. Duration of developing a DHR was (mean $\pm$ SD) 5.37 ± 14.28 days for Type I hypersensitivity reactions. Duration of developing a DHR was 34.12 ± 37.79 days for Type IV hypersensitivity reactions.

Discontinuation of the current treatment regimen was considered sufficient in 43 (29%) patients who developed a hypersensitivity reaction. Treatment of 58 (39.2%) patients were interrupted and they were administered antihistamines, treatment of 3 (2.1%) were interrupted and they were administered oral/parenteral steroids. For 44 (29.7%) patients, antihistamines and oral/parenteral steroids were administered simultaneously. No anaphylaxis was observed in any patient that required the administration of adrenaline and oxygen support. Discontinuation of the current treatment regimen was considered sufficient in 29 of 91 patients (29%) who developed a Type I hypersensitivity reaction. Treatment of 40 (44%) patients were interrupted and they were administered antihistamines, treatment of 1 (1%) were interrupted and they were administered oral/parenteral steroids. For 21 (23%) patients, antihistamines and oral/parenteral steroids were administered simultaneously. Discontinuation of the current treatment regimen was considered sufficient in 14 of 56 patients (25%) who developed a Type IV hypersensitivity reaction. Treatment of 18 (32%) patients was interrupted and they were administered antihistamines, treatment of 2 (4%) were interrupted and they were administered oral/parenteral steroids. For 22 (39%) patients, antihistamines and oral/parenteral steroids were administered simultaneously.

The number of patients who developed only Type I hypersensitivity reactions, only Type IV hypersensitivity reactions and both Type I and Type IV hypersensitivity reactions while receiving standard antituberculosis treatment were 81, 47, and 1, respectively. The number of patients who developed only Type I hypersensitivity reactions while

receiving nonstandard antituberculosis treatment were 10 and this figure was nine for patients who developed only Type IV hypersensitivity reactions.

Type I hypersensitivity reactions were observed in 78 of 123 (63.5%) drug-sensitive patients, Type IV hypersensitivity reactions were observed in 44 of 123 (35.7%) drug-sensitive patients. Type I and Type IV hypersensitivity reactions were simultaneously observed in 1 of 123 (0.8%) drug-sensitive patients. Standard antituberculosis treatment of 68 (55.2%) drug-sensitive patients was successfully completed with desensitization. The duration of treatment in this patient group was 7.1 ± 1.3 months. Desensitization was successfully completed in 10 (8.1%) drug-sensitive patients, but their regimen was changed due to hepatotoxicity. The duration of treatment in this patient group was 7.5 ± 2.1 months. In 45 (36.7%) drug-sensitive patients, desensitization was initiated with the standard regimen; however, the drug in the regimen was updated as the patient could not tolerate. For this group of patients, the desensitization process was successfully completed after updating the drug in the regimen. The duration of treatment in this patient group was 9.5 ± 3.5 months. As a result; of these 123 drug-sensitive patients, 99 (80.4%) completed the treatment successfully, 1 (0.8%) patient failed the treatment, 2 (1.6%) patients were not currently followed up, 4 (3.2%) patients died, 17 (14%) were still under treatment [Table 4].

Type I hypersensitivity reaction was observed in 13 (52%) of 25 drug-resistant patients and Type IV hypersensitivity reaction was observed in 12 (48%) of the patients. Drug resistance was examined in two groups: patients with isoniazid resistance (without accompanying rifampicin resistance) were evaluated in one group. Rifampicin resistant/multi-drug resistant tuberculosis, preextensively drug-resistant tuberculosis (isoniazid, rifampicin, and quinolone resistance) and extensively drug-resistant tuberculosis (resistance to isoniazid, rifampicin, quinolone, and

Table 3: Type of hypersensitivity and responsible drugs

Responsible drug	Type of hypersensitivity reaction								Total
	Type I			Type IV			Type I + IV		
	Female	Male	Total	Female	Male	Total	Female	Male	
Isoniazid	4	1	5	4	-	4	-	-	9
Rifampicin	5	1	6	5	4	9	-	-	15
Ethambutol	1	3	4	-	1	1	-	-	5
Pyrazinamide	9	9	18	2	4	6	-	1	25
Streptomycine	-	-	-	-	-	-	-	-	-
Levofloxacin	-	-	-	-	-	-	-	-	-
Moxifloxacin	-	1	1	1	1	2	-	-	3
Kapreomycin	-	-	-	-	-	-	-	-	-
Amikacin	-	-	-	-	2	2	-	-	2
Pas	-	2	2	-	1	1	-	-	3
Prothionamide	-	1	1	-	1	1	-	-	2
Cycloserine	1	-	1	-	2	2	-	-	3
Linezolid	1	-	1	-	-	-	-	-	1
Total	21	18	39	12	16	28	-	1	68

bedaquiline or linezolid) together were evaluated in the second group. Desensitization could be successfully completed with the originally planned treatment regimen in both classifications. The duration of treatment for patients with isoniazid resistance (not accompanied by rifampicin resistance) was 17.5 ± 9.1 months. The duration of treatment for patients with rifampicin resistance/multi-drug-resistant tuberculosis, preextensively drug-resistant tuberculosis (isoniazid, rifampicin, and quinolone resistance) and extensively drug-resistant tuberculosis (resistance to isoniazid, rifampicin, quinolone, and bedaquiline or linezolid) was 18 ± 0 months. As a result; of these 25 drug-resistant patients, 15 (60%) completed the treatment successfully, 1 (4%) patient failed to come back for follow-up examinations, 6 (24%) patients were still under treatment and 3 (12%) patients went abroad for organ transplantation [Table 5].

CONCLUSION

The exact incidence of hypersensitivity reactions developed due to antituberculosis drugs is yet unknown. In a limited single-center cohort study conducted in our country, the incidence was reported as 3.43%.^[14] Within the literature review conducted by Prasad *et al.*, the rate of developing hypersensitivity to first-generation antituberculosis drugs was reported as between 8% and 85%, and the rate of developing hypersensitivity to secondary drugs was between 69% and 96%.^[15] Our health-care institution is located in a big metropolis like İstanbul, which is the most populous city of our country. It is the largest health care institution where multi-drug resistant tuberculosis patients are hospitalized. The prevalence of DHRs in inpatients herein was calculated as 7.8%.

Adverse drug reactions are generally more common in females.^[16,17] Women's lower body weight, smaller organ sizes, greater body fat, gastric motility differences, and lower glomerular filtration rate are thought to be affecting adverse drug reactions.^[16] Logistic regression analysis performed within the scope of our study revealed that the prevalence of hypersensitivity reactions was higher in women patients.

Particularly for elderly patients, the prevalence of adverse drug reactions is higher. The risk, which is mainly attributed to isoniazid and rifampicin, further increases in patients over 60 years of age.^[18] In the etiology, simultaneous use of multiple drugs and a decrease in the ability of the kidney to remove drugs from the body are considered.^[16] The majority of patients in this study (42 patients [28.4%]) were in the age group of 51–65 years. The mean age of our patients was 47.2 ± 18.95 ; this finding was similar to the mean age of 45.8 ± 16.2 ^[4] reported by Tan *et al.* and the mean age of 40.79 ± 16.79 ^[19] reported by Sood *et al.*

The hypersensitivity reaction was concluded to be higher in patients who were citizens of the Republic of Turkey and who were born in the Asian Continent. Similarly, Yee *et al.* observed that the prevalence of adverse drug reactions developed against primary antituberculosis agents was associated with being born in Asia.^[18] Higher prevalence of adverse drug reactions developed against primary antituberculosis agents in Asian patients was attributed genetically to some HLA sequences.^[20] We also agree with the conclusion that the higher prevalence of hypersensitivity reactions developed against primary drugs by patients from the Asian population may be attributed to certain HLA sequences.

Table 4: Hypersensitivity reaction and treatment outcomes in drug sensitive patients

Originally planned treatment	Hypersensitivity reaction			Final treatment	Treatment duration (months)	Treatment result, n (%)
	Type I, n (%)	Type IV, n (%)	Type I + Type IV, n (%)			
Drug sensitive (n: 123)	48 (39)	20 (16.2)	Ø	Standard treatment	7.1±1.3	1. Treatment success: 99 (80.4)
	7 (5.7)	3 (2.4)	Ø	Regimen change due to hepatotoxicity	7.5±2.1	2. Treatment failure: 1 (0.8)
	23 (18.8)	21 (17.1)	1 (0.8)	Regimen change due to drug allergy	9.5±3.5	3. Nonfollow-up: 2 (1.6)
Total	78 (63.5)	44 (35.7)	1 (0.8)			4. Died: 4 (3.2)
						5. Still under treatment: 17 (14)
						6. Traveled abroad for transplantation: Ø
						123 (100)

Table 5: Hypersensitivity reaction and treatment outcomes in drug resistant patients

Originally planned treatment Drug resistant (n: 25)	Hypersensitivity reaction		Final treatment	Treatment duration (months)	Treatment result, n (%)
	Type I, n (%)	Type IV, n (%)			
Isoniazid resistance (w/o accompanying rifampicin resistance) (n: 3)	2 (8)	1 (4)	No regimen change due to drug allergy	17.5±9.1 months	1. Treatment success: 15 (60)
RD/ÇİD/Pre-YİD TB (n: 22)	11 (44)	11 (44)	Ø	18±0 months	2. Treatment failure: Ø
			Ø		3. Nonfollow-up: 1 (4)
					4. Died: Ø
					5. Still under treatment: 6 (24)
					6. Traveled abroad for transplantation: 3 (12)
Total (25)	13 (52)	12 (48)			25 (100)

TB: Tuberculosis, RR: Rifampicin resistant, MDR: Multidrug resistant, EDR: Extensively Drug Resistant

Drug hypersensitivity was statistically significantly higher in newly diagnosed tuberculosis patients who had not received any antituberculosis treatment before. We think that this result is attributable to the higher number of newly diagnosed tuberculosis patients. There are publications defending similar views in the literature. For example, all of the patients included in the study conducted by Siripassorn *et al.* were newly diagnosed tuberculosis patients.^[21] The study performed by Javadi *et al.* revealed that the risk of developing adverse reactions was higher in men who had not been treated for tuberculosis before.^[22]

Previous use of beta-lactam group antibiotics is found to be elevating the risk for IgE-mediated hypersensitivity.^[23] However, IgE-mediated hypersensitivity reaction is not mentioned in quinolone group antibiotics, mast cells are degranulated by direct stimulation. Therefore, in the use of quinolone antibiotics, a reaction occurs at any dose, including the first dose.^[24] There are studies in the literature concerning the medications used in antituberculosis treatment, in particular rifampicin. The presence of antirifampicin antibodies against rifampicin has been demonstrated. These antibodies are structured as IgG and IgM and they cause Type III hypersensitivity reactions.^[25-27] Reactions induced by these antibodies are more likely associated with the intermittent regimen; however, cutaneous reactions are attributed to daily use. In addition, attention has been drawn to the presence of IgE antibodies against rifampicin in patients experiencing rifampicin-susceptible anaphylaxis. One study examining the patients who had experienced rifampicin-susceptible anaphylaxis reported that anaphylaxis was experienced in the 1st day by the patient who was administered the daily doses, whereas it was reported that anaphylaxis occurred at 20 months in another patient who received monthly doses. Medications other than Rifampicin used in the antituberculosis treatment may also cause hypersensitivity reactions by directly stimulating the mast cell, just like quinolones. Further studies are required in this regard.

It was concluded that the risk of developing hypersensitivity is higher in patients without bacteriological diagnosis of tuberculosis, which is in patients with histopathological diagnosis. There was no significant difference in terms of pulmonary and extrapulmonary involvement. This finding is interesting. In fact, we see that the prevalence of adverse drug reactions is higher, particularly in extrapulmonary tuberculosis.^[28-30]

The most common agent responsible for hypersensitivity reactions is pyrazinamide, followed by rifampicin, isoniazid, and ethambutol. Rifampicin or pyrazinamide has been reported in different sources as the most frequently responsible agent for allergy.^[31-34] Tan *et al.* and Yee *et al.* reported pyrazinamide as the most frequently responsible agent for allergy.^[4,18] The findings of our study revealed that the most common agent responsible for Type I hypersensitivity was pyrazinamide and the most common agent responsible for Type IV hypersensitivity was

rifampicin. Multi-drug allergy was observed in 11 (21.1%) of 52 patients in whom the responsible drug could be identified. Multiple sensitivities against antituberculosis drugs have been reported in some studies in the literature.^[33,35] Sharma *et al.* reported the prevalence of multi-drug allergy as 25%.^[36]

DHR developed in all patients (mean $\pm$ SD) at 16.41 ± 29.24 days. It developed between 0 days and 150 days. The duration of developing a DHR was (mean $\pm$ SD) 5.37 ± 14.28 days for Type I hypersensitivity reactions. The duration of developing a DHR was 34.12 ± 37.79 days for Type IV hypersensitivity reactions. The findings of our study were compatible with the literature.^[5]

The most frequently used solutions in patients who developed a hypersensitivity reaction were interruption of treatment, antihistamine treatment, steroid treatment, or their combinations. Some authors prioritize steroid therapy. Steroid therapy is used prominently, particularly for severe drug reactions.^[37] We, too, prioritize steroid therapy in case of severe reactions. Steroid use remained low throughout this study due to the low rate of patients who were included in this study and developed severe drug reactions. This gives us the opportunity to perform diagnostic tests such as skin prick tests and intradermal tests earlier and to initiate the treatment earlier.

The most frequently manifested hypersensitivity reaction is Type I hypersensitivity reaction which includes urticaria. This is followed by Type IV hypersensitivity reactions including maculopapular drug eruption. Maculopapular drug eruption is more commonly examined in some studies.^[5,35] Severe reactions such as anaphylaxis, Stevens–Johnson syndrome, TEN, and AGEP are very rare;^[5] these were neither observed in our study. We believe that the safety profile of drugs used in antituberculosis treatment in the context of hypersensitivity reactions is good.

For the purpose of assessing the treatment results, we examined our patients in two separate groups as drug sensitive and resistant. Concerning the treatment results, 99 (80.4%) of 123 drug-sensitive patients along with 15 (60%) of 25 drug-resistant patients successfully completed the treatment. The patients who were considered to have successfully completed the treatment consisted of patients who developed drug-susceptible hypersensitivity under antituberculosis treatment however successfully completed the treatment regimen at the end of a desensitization process applied within the scope of the inpatient treatment. No significant increase in the duration of treatment monthly was in question in both drug-sensitive and drug-resistant patients.

Antituberculosis treatment is applied in our country as a directly supervised treatment. Manifestation of hypersensitivity reactions to antituberculosis drugs under the supervision of a physician and health-care professional provides the advantage of being recognized earlier. There are still deficiencies that need to be improved in the management of hypersensitivity reactions that may develop during the antituberculosis treatment; in this context, safe, standardized approaches are required. Thus,

patient compliance will be improved and the risk of developing resistant tuberculosis will be reduced globally.^[38]

In conclusion, we suggest health-care professionals to follow their patients more closely, particularly in the early phase of treatment, to recognize and treat possible hypersensitivity reactions that may develop in the case of a disease such as tuberculosis earlier. Performing diagnostic tests on patients who have developed a hypersensitivity reaction and administering all the drugs through a desensitization process by leaving the positive agent to the end is essential for patient compliance and success of treatment. However, we believe that the compliance of the patients to the antituberculosis treatment has been improved at the end of appropriate management of hypersensitivity reactions and the treatment results in success.

Ethics approval and consent to participate

Ethics committee approval of the University of Health Sciences, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital was obtained for this study (dated June 03, 2021, protocol code: 116.2017.R-225).

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Conflicts of interest

There are no conflicts of interest.

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