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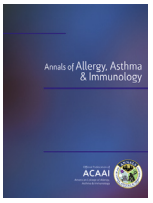

Immediate-type hypersensitivity reactions due to antituberculosis drugs: a successful readministration protocol

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ABSTRACT

Background: Little is known about drug hypersensitivity reactions from antituberculosis drugs.
Objective: To determine the frequency, risk factors, and characteristics of immediate-type hypersensitivity reactions from first-line antituberculosis drugs and to evaluate the usefulness of a readministration protocol for culprit drugs in this group of patients.
Methods: The study population consisted of patients with tuberculosis who were hospitalized and treated in the authors' hospital in 2011. Demographics and disease and treatment characteristics of patients with immediate-type hypersensitivity from antituberculosis drugs were compared with the other patients. Culprit drugs were readministered gradually according to a defined protocol to patients with immediate-type hypersensitivity.
Results: Tree hundred seventy-nine patients were included in the study. Eighteen immediate-type hypersensitivity reactions were detected in 13 patients (3.43%). The only identified risk factor was female sex (odds ratio 4.085). Isoniazid, rifampicin, pyrazinamide, and ethambutol were readministered in 11 patients and rifampicin was readministered in 2 patients, with 6- to 8-step protocols for each drug. Only in 2 patients did allergic reactions with rifampicin develop during the procedure. In these patients, after treatment and complete remission of allergic symptoms, the last tolerated dose was administered and the protocol was completed with the same adjustments.
Conclusion: Immediate-type allergic reactions from antituberculosis drugs are not rare and not related to disease or treatment characteristics. The protocols used in this study provide a useful and safe method for readministration of culprit drugs to patients with antituberculosis drug hypersensitivity.
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Introduction

Tuberculosis is a serious public health threat unless it is treated properly. The goals of treatment are to ensure cure without relapse, to prevent death, and to impede transmission. However, tuberculosis chemotherapy is complicated by the need for multidrug regimens that need to be administered regularly over long periods. Adverse drug reactions are one of the most common reasons for chemotherapy failure,[1,2] because they cause treatment interruption.

Drug hypersensitivity reactions from antituberculosis drugs are not well known because the quality of data on this topic is very low. Even in studies aiming to show the adverse events associated with antituberculosis drugs, drug hypersensitivity reactions were not defined in detail. Some of these studies mentioned only cutaneous lesions, whereas others did not provide any information about drug hypersensitivity reactions. Also, differences in study design, studied groups, and data presentation make it difficult to comment on this topic.[1,3–8] There is a need for management strategies for drug hypersensitivity reactions from antituberculosis drugs that are classified as immediate- or non-immediate–type drug hypersensitivity reactions according to international guidelines.[9,10] The limited number of drugs used in tuberculosis chemotherapy increases the importance of this requirement.

The aim of this study was to determine the prevalence, risk factors, and characteristics of immediate-type drug hypersensitivity reactions from first-line antituberculosis drugs and to evaluate the usefulness of a readministration protocol for culprit drugs.

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Methods

Study Population

Patients with tuberculosis who were hospitalized and treated in the authors' hospital from January 1, 2011 through December 31, 2011 were included in the study. The study population consisted of 2 groups.

Group A consisted of patients with tuberculosis who were referred to the authors' allergy clinic and diagnosed as having an immediate-type drug hypersensitivity reaction from antituberculosis drugs. Demographics, drug allergy history, tuberculosis disease, and treatment characteristics of these patients were noted.

Immediate-type drug hypersensitivity reaction was defined as an allergic reaction within 1 hour after consumption of the drugs, such as flushing, urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea), decrease in blood pressure, or cardiovascular collapse.[9] Symptoms that occurred during the drug hypersensitivity reaction also were noted and graded according to the classification of Ring and Messmer[11] (Table 1). After the treatment of allergic reactions, the culprit antituberculosis drugs were readministered to patients in accordance with the protocols described below (Table 2). Patients were followed until the end of their treatment. Only 1 patient dropped out from follow-up shortly after the second month of treatment (Table 1).

Group B consisted of patients with tuberculosis who were treated in the authors' hospital during the same period and who did not have drug hypersensitivity reactions. This group was designated the control group for group A. In July 2012, their files were screened for demographics, drug allergy history, tuberculosis disease, and treatment characteristics.

Excluded from the study were patients who were treated with second-line antituberculosis drugs, were treated for non-tuberculosis mycobacterium infection, or had insufficient file information.

Protocol Used for Readministration of Culprit Drugs in Group A

Readministration of each drug was attempted with 6- to 8-step regimens on consecutive days. The regimens were initiated with 7.5, 10, 10, and 5 mg of isoniazid, rifampicin, pyrazinamide, and ethambutol, respectively. In each regimen, drug doses were given at a maximum 2.5-fold increase every 30 minutes. Only the interval between the next to last dose and the last dose was 60 minutes. All regimens were implemented to ensure tolerance to the therapeutic dosage of each drug before advancing to the next drug on the consecutive day. Each day, before starting a new drug application, the therapeutic dose for the drug or drugs that were administered on previous days were given to the patient. Then, the regimen for the application of the next drug was launched (Table 2). The procedure was performed under close observation with one-on-one nurse-to-patient care. Symptoms, vital signs, and physical examination findings were observed. When an allergic reaction occurred during the procedure, drug administration was suspended and the reaction was treated according to international guidelines.[12,13] After complete remission of the allergic symptoms, the last tolerated dose was administered and the protocol was completed with the same adjustments.

This study was approved by the ethical board of the Keçiören Training and Research Hospital (Ankara, Turkey). Patients were informed about the readministration protocol and they provided written informed consent.

Parameters Investigated and Presented in the Study

Groups A and B were compared for demographics, drug allergy history, tuberculosis disease, and treatment characteristic to examine possible risk factors for immediate-type drug hypersensitivity reactions. In this study, tuberculosis was defined according to World Health Organization recommendations.[14] Patients also were classified as having pulmonary tuberculosis and/or extrapulmonary tuberculosis. To investigate the link between drug hypersensitivity reactions and intermittent or discontinuous treatments, patients who had interrupted therapy for any reason before an allergic reaction were noted.

The details of the data obtained from readministration protocols also were noted.

Statistical Analysis

All analyses were performed using SPSS 11.0 (SPSS Inc, Chicago, Illinois). Differences in proportion were analyzed by the χ^2 test. Differences in means were evaluated by the Mann-Whitney U test. As a measurement for relative risk, odds ratios and 95% confidence intervals were calculated.

Results

Characteristics of Study Group

In 2011, 563 patients with tuberculosis were hospitalized and treated in the authors' hospital. Of these, 118 patients who were treated with second-line antituberculosis drugs, 5 patients treated for non-tuberculosis mycobacterium infection, 61 patients who had insufficient file information were excluded. The remaining 379 patients (139 women and 240 men) composed the study group.

The patients' age (mean $\pm$ SD) was 45.39 $\pm$ 17.36 years. Of these, 290 patients (76.5%) had pulmonary tuberculosis, 63 (16.6%) had extrapulmonary tuberculosis, and 26 (6.9%) patients had pulmonary and extrapulmonary tuberculosis.

All 379 patients were treated with isoniazid and pyrazinamide, 378 patients were treated with rifampicin and ethambutol, and 40 patients were treated with streptomycin. During this period, isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin were used actively for 59,046, 59,057, 29,448, 35,993, and 1,912 days, respectively.

Prevalence and Risk Factors for Immediate-Type Drug Hypersensitivity Reactions

Immediate-type drug hypersensitivity reactions were detected in 13 patients (3.43%). When the 2 study groups' characteristics were compared for possible risk factors, only female sex was found to be a risk factor (odds ratio 4.08, 95% confidence interval 1.23–13.52, $P = .018$; Table 3).

Characteristics of Immediate-Type Drug Hypersensitivity Reactions

Eighteen reactions were detected in 13 patients (9 patients had 1 reaction, 3 patients had 2 reactions, and 1 patient had 3 reactions). The reason for the recurrent reactions was the reintroduction of the culprit drugs one at a time or one by one before referral to the allergy clinic. For some patients (cases 5–10), the primary physicians also tried to continue the antituberculosis treatment with antihistamines and/or systemic steroids after the drug hypersensitivity reactions but were not successful. The symptoms were resolved after cessation of the antituberculosis treatments in these patients (Table 1).

Of these 18 reactions, 15 occurred during isoniazid, rifampicin, pyrazinamide, and ethambutol therapy; 1 during isoniazid, rifampicin, and ethambutol therapy; and 2 during rifampicin therapy. Cutaneous symptoms, such as flush with pruritus, urticaria, and angioedema, were detected in all reactions. Gastrointestinal symptoms, such as nausea and vomiting, accompanied cutaneous lesions in 4 patients, and rhinitis, conjunctivitis, and dizziness were detected in 1 patient. The symptom characteristics of each patient

Table 1
Characteristics of patients with drug hypersensitivity reactions

Case number	Reactions, n	Culprit drugs	Symptoms and signs	Reaction grade	Special notes for hypersensitivity reactions seen in cases	Readministered drugs	Readministration reaction	Days patients followed after protocol
1	1	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria	1		isoniazid, rifampicin, pyrazinamide, ethambutol	—	181
2	1	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria	1		isoniazid, rifampicin, pyrazinamide, ethambutol	—	180
3	1	isoniazid, rifampicin, pyrazinamide, ethambutol	flush with pruritus, nausea, vomiting	3		isoniazid, rifampicin, pyrazinamide, ethambutol	—	248
4	1	isoniazid, rifampicin, pyrazinamide, ethambutol	flush with pruritus, angioedema	1		isoniazid, rifampicin, pyrazinamide, ethambutol	—	190
5	1	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria	1	antituberculosis treatment could not be sustained despite antihistamine therapy	isoniazid, rifampicin, pyrazinamide, ethambutol	—	263
6	1	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria, angioedema, rhinitis	2	antituberculosis treatment could not be sustained despite antihistamine therapy	isoniazid, rifampicin, pyrazinamide, ethambutol	positive with rifampicin	169
7	1	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria	1	antituberculosis treatment could not be sustained despite antihistamine therapy	isoniazid, rifampicin, pyrazinamide, ethambutol	—	174
8	1	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria	1	antituberculosis treatment could not be sustained despite antihistamine and steroid therapy	isoniazid, rifampicin, pyrazinamide, ethambutol	—	190
9	1	isoniazid, rifampicin, pyrazinamide, ethambutol	flush with pruritus, nausea, vomiting	3	antituberculosis treatment could not be sustained despite antihistamine and steroid therapy	isoniazid, rifampicin, pyrazinamide, ethambutol	—	72
10	1	isoniazid, rifampicin, pyrazinamide, ethambutol	flush with pruritus	1		isoniazid, rifampicin, pyrazinamide, ethambutol	—	186
	2	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria	1	antituberculosis treatment could not be sustained despite antihistamine therapy			
11	1	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria, angioedema	1		rifampicin	positive with rifampicin	180
	2	rifampicin	urticaria	1				
12	1	isoniazid, rifampicin, ethambutol	urticaria	1		rifampicin	—	234
	2	rifampicin	urticaria, angioedema	1				
13	1	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria, nausea, dizziness	2				178
	2	isoniazid, rifampicin, pyrazinamide, ethambutol	urticaria	1		isoniazid, rifampicin, pyrazinamide, ethambutol	—	
	3	isoniazid, rifampicin, pyrazinamide, ethambutol	flush with pruritus, nausea, conjunctivitis	2		isoniazid, rifampicin, pyrazinamide, ethambutol	—	

Table 2
Readministration protocol used in the study

Day 1			Day 2			Day 3			Day 4			Day 5		
Time	Drug dose	mg	Time	Drug dose	mg	Time	Drug dose	mg	Time	Drug dose	mg	Time	Drug dose	mg
	isoniazid		08:00	isoniazid	300	08:00	isoniazid + rifampicin	300 + 600	08:00	isoniazid + rifampicin + pyrazinamide	300 + 600 + 2,000	8:00	isoniazid + rifampicin + pyrazinamide + ethambutol	300 + 600 + 2,000 + 1,500
09:30	solution A[a] 1 mL	7.5		rifampicin			pyrazinamide			ethambutol				
10:00	solution A 2 mL	15	09:30	solution C[c] 1 mL	10	09:30	solution E[e] 2 mL	10	09:30	solution G[g] 1 mL	5			
10:30	solution A 3 mL	22.5	10:00	solution C 2 mL	20	10:00	solution E 4 mL	20	10:00	solution G 2 mL	10			
11:00	1/8 tablet of isoniazid	37.5	10:30	solution C 5 mL	50	10:30	solution E 8 mL	40	10:30	solution G 4 mL	20			
11:30	¼ tablet of isoniazid	75	11:00	solution B[b] 5 mL	100	11:00	solution E 16 mL	80	11:00	solution G 8 mL	40			
12:30	½ tablet of isoniazid	150	11:30	solution B 10 mL	200	11:30	solution D[d] 3 mL	150	11:30	solution F[f] 2 mL	100			
			12:30	solution B 11 mL	220	12:00	solution D 4 mL	200	12:00	solution F 4 mL	200			
						12:30	1 tablet of pyrazinamide	500	12:30	1 tablet ethambutol	500			
						13:30	2 tablets of pyrazinamide	1,000	13:30	1 + ¼ tablets of ethambutol	625			

[a] A suspension was prepared by crushing 1 tablet of isoniazid (300 mg) into a volume of 40 mL of 0.9% NaCl to a final concentration of 7.5 mg/mL.
[b] A suspension was prepared by mixing the content of 1 capsule of rifampicin (600 mg) into a volume of 30 mL of 0.9% NaCl to a final concentration of 20 mg/mL.
[c] A suspension was made by 1:2 dilution of solution B to a final concentration of 10 mg/mL.
[d] A suspension was prepared by crushing 1 tablet of pyrazinamide (500 mg) into a volume of 10 mL of 0.9% NaCl to a final concentration of 50 mg/mL.
[e] A suspension was made by 1:10 dilution of solution D to a final concentration of 5 mg/mL.
[f] A suspension was prepared by crushing 1 tablet of ethambutol (500 mg) into a volume of 10 mL of 0.9% NaCl to a final concentration of 50 mg/mL.
[g] A suspension was made by 1:10 dilution of solution F to a final concentration of 5 mg/mL.

with a drug hypersensitivity reaction are listed in Table 1. According to the classification of Ring and Messmer,[11] the reaction severities were grade 1 in 13 patients (72.2%), grade 2 in 3 patients (16.7%), and grade 3 in 2 patients (11.1%; Table 1).

Results of Drug Readministration

Isoniazid, rifampicin, pyrazinamide, and ethambutol were readministered in 11 cases and rifampicin was readministered in 2 cases according to the described protocols. During the procedure, only 2 patients had allergic reactions (Table 1).

In the first case (case 11), mild facial erythema was seen 40 minutes after the last dose (220 mg) of rifampicin. The reaction resolved spontaneously in 20 minutes. After resolution of all symptoms, 220 mg was repeated and no reaction was observed. The patient tolerated the full dose of the drug (600 mg) on the next day.

The second case (case 6) developed throat and ear pruritus, dyspnea, and cough 30 minutes after 200 mg of rifampicin. After application of 45.5 mg of pheniramine, 40 mg of methyl prednisolone, and 2.5 mg of nebulized salbutamol, the dyspnea and cough resolved but palmar erythema developed 35 minutes later. Pheniramine was repeated and 10 mg of montelukast was given. After resolution of all symptoms, 100 mg of rifampicin was readministered and then the protocol was completed without difficulty. The patient tolerated the full dose of the drug (600 mg) on the next day.

In case 13, 39 days after the readministration protocol, antituberculosis drugs were discontinued because of the elevation of hepatic enzymes. After recovery, the antituberculosis drugs were restarted as full doses by the patient's primary physician. Owing to the recurrence of the allergic reaction with symptoms of flush with pruritus, nausea, and conjunctivitis, the patient was referred to the authors' clinic for the second time. The culprit drugs were readministered for the second time according to the protocol without any reactions.

The readministration protocol allowed the patients to resume isoniazid, rifampicin, pyrazinamide, and ethambutol without further signs and symptoms of hypersensitivity for 70 to 263, 67 to 261, 40 to 72, and 38 to 71 days, respectively.

Discussion

This is the first systematic study designed to evaluate the prevalence and risk factors of immediate-type drug hypersensitivity reactions from antituberculosis drugs. It also provides a strategy for the management of these patients. The study showed that immediate-type drug hypersensitivity reactions from antituberculosis drugs are not rare (3.43%) and are independent of the disease and treatment characteristics. The only risk factor found was female sex. The readministration strategy used in this study seemed to be effective and safe.

Data for the prevalence of drug hypersensitivity reactions from antituberculosis drugs are based mostly on studies evaluating all adverse events together. In these studies, the prevalence of cutaneous lesions was reported to be approximately 5% to 16%.[1,2,4–6,15] However, these studies reported only the prevalence values for cutaneous lesions. Accompanying symptoms to cutaneous lesions were not mentioned. Also, the timing and characteristics of the lesions were not defined in detail but were mentioned only as "rash," "exanthema," "cutaneous lesions," or "pruritus."[1,3,4,16] In a study focusing on cutaneous reactions from first-line antituberculosis drugs, Tan et al[7] detected cutaneous adverse drug reactions in 5.7% of patients. The reactions were mostly in morbilliform rush form (72.3%) and urticaria (8.5%). Unlike previous studies, the present study has presented a prevalence rate for immediate-type hypersensitivity reactions, which was 3.4%. Furthermore, the present study has presented data on the severity of these reactions.

Table 3
Comparison of drug hypersensitivity in DHSR-positive and DHSR-negative groups

	DHSR-negative group	DHSR-positive group	OR (95% CI)	*P* value
Sex, n (%)			4.08 (1.23–13.52)	.018
Women	130 (93.5)	9 (6.5)		
Men	236 (98.3)	4 (1.7)		
Age (y), mean ± SD	45.62 ± 17.40	38.85 ± 15.21		>.005
Drug allergy history, n (%)				>.005
Positive	7 (100)	0 (0)		
Negative	306 (96.8)	10 (3.2)		
Diagnosis, n (%)				>.005
Pulmonary tuberculosis	282 (97.2)	8 (2.8)		
Extrapulmonary tuberculosis	60 (95.2)	3 (4.8)		
Pulmonary + extrapulmonary tuberculosis	24 (92.3)	2 (7.7)		
Case identification, n (%)				>.005
New case	315 (97.2)	9 (2.8)		
Other[a]	51 (92.7)	4 (7.3)		
Drug interruption, n (%)				>.005
Yes	88 (94.6)	5 (5.4)		
No	278 (97.2)	8 (2.8)		

Abbreviations: CI, confidence interval; DHSR, drug hypersensitivity reaction; OR, odds ratio.
[a]Treatment after failure, return after default, or relapse.

Although most immediate-type drug hypersensitivity reactions from antituberculosis drugs were mild, grade 3 reactions were detected.

When dealing with drug hypersensitivity reactions, it is important to identify patients who are at risk. The only well-defined risk factor for antituberculosis drug hypersensitivity is seropositivity to human immunodeficiency virus.[17,18] The best example of this is the development of thiacetazone-associated non-immediate–type drug hypersensitivity reactions seen as Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with human immunodeficiency virus. Human immunodeficiency viral seropositivity also has been associated with non-immediate–type drug hypersensitivity reactions from first-line antituberculosis drugs.[1]

In the present study, the only risk factor for immediate-type drug hypersensitivity reactions was female sex (odds ratio 4.08). In general, female sex is a known risk factor for drug allergies.[19] From the standpoint of antituberculosis drugs, female sex has been associated with the development of drug-induced cutaneous reactions in 2 other studies.[2,5] Although not conclusive, these data suggest the need for close monitoring of female patients during treatment of tuberculosis.

The principle of tuberculosis therapy depends on multidrug regimens. Schaberg et al[2] reported that the most common causes for drug removal from treatment were hepatotoxicity and development of exanthema. Management strategies for hepatotoxicity is well defined.[14,20] Likewise, there is a need for a management strategy for drug hypersensitivity reactions.

The general principle in the management of drug hypersensitivity reactions is finding safe alternatives for the culprit drugs.[21] However, the limited number of drugs used in tuberculosis chemotherapy complicates the management of drug hypersensitivity reactions from antituberculosis drugs.

First, in the treatment of tuberculosis, all drugs are usually taken at 1 time, so it is not possible to establish the responsible drug from the patient's history. Drugs can be reintroduced with drug provocation tests to establish causality. However, this approach increases the risk of inducing additional hypersensitivity reactions. Lehloenya et al[22] investigated antituberculosis drug reintroduction in patients who developed cutaneous reactions. Half the patients had reintroduction reactions and 52% of reactions were moderate to severe. In addition to leading the reoccurrence of the reaction, this strategy causes a further delay in starting treatment owing to the time needed for treatment of the repeated reaction.

Second, although the responsible drug could be found using drug provocation tests, the culprit drug cannot be easily removed from the treatment regimen because the number of first-line drugs is limited and treatment with second-line drugs is less effective, has additional toxicity, and requires longer treatment periods.[23]

For these reasons, although drug provocation testing has the advantage of establishing the culprit drug, it does not seem to be the optimal method for the management of patients with tuberculosis and immediate-type drug hypersensitivity reactions. The priority in this group of patients was to achieve a fast but safe method of providing reuse of drugs, rather than finding the responsible drug. Aberer and Kranke[21] recommended a similar approach and suggested desensitization rather than detailed allergy testing as the initial method in patients who have cystic fibrosis or tuberculosis, in which the drug concerned is more effective than the alternatives.

Therefore, in this study, the culprit drugs were reintroduced with gradually increasing dose protocols consisting of 6 to 8 steps on consecutive days to induce tolerance. It would not be accurate to recognize this procedure as a desensitization protocol for each drug because the presence of drug hypersensitivity reactions and the responsible drug were not been determined definitively with drug provocation tests. However, there are reasons to believe that these patients were allergic to at least 1 of these drugs and that the protocol led the development of tolerance in these patients. Four patients had multiple reactions with the culprit drugs, and the other 5 patients were unable to tolerate the culprit drugs despite systemic steroid and/or antihistamine therapy. Also, in 2 patients who had allergic reactions with rifampicin during the procedure, the approaches used in desensitization could overcome the reaction.

Antituberculosis drug desensitization data have been reported in the literature[24–27]; however, standard protocols could not be created. The only institutional protocol, which was proposed by the Japanese Society for Tuberculosis, is a 16-day slow desensitization protocol. This protocol was used by Kobashi et al[28] in drug fever and/or eruption cases and found to be successful in approximately 80% of cases.

For immediate-type drug hypersensitivity reactions such as in the present study group, rapid desensitization protocols are recommended.[13] Rapid desensitization with antituberculosis drugs was applied for first time by Holland et al.[24] Based on this protocol, Matz et al[29] identified desensitization schemes for rifampicin and ethambutol that were tested in 10 patients, but the patient group was not homogeneous and consisted of immediate-type and

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non-immediate–type drug hypersensitivity reactions and the protocol was not successful in 5 of the 10 patients. The present study is the first study evaluating the usefulness of a rapid tolerance induction protocol in a well-defined, homogeneous group of drug hypersensitivity cases from antituberculosis drugs. The protocol used in this study enabled the reuse of drugs in all cases, with a complete success rate. The study showed that the protocol is not only effective but also safe. The hypersensitivity reactions seen during the procedure were mild and could be easily controlled. Recently, in 2 patients with immediate-type drug hypersensitivity reactions, successful desensitizations with isoniazid and pyrazinamide were reported.[30,31] The protocols used in these 2 cases were very similar to the present protocol, with small differences, thus supporting the usefulness of the present protocol.

In conclusion, this study is the first to systematically analyze immediate-type drug hypersensitivity reactions from first-line antituberculosis drugs. Clues for prevalence and risk factors were obtained in this study. A safe, useful, rapid strategy for reintroduction of culprit drugs was demonstrated.

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