Original paper

# Delayed drug hypersensitivity to anti-tuberculosis drug: a new desensitization scheme

**İsmet Bulut[1], Zeynep Yegin Katran[1], Aylin Babalık[2], Metin Keren[1], Fatma Merve Tepetam[1]**

[1]Department of Allergy and Immunology, University of Health Sciences, Süreyyapaşa Training and Research Hospital, Istanbul, Turkey
[2]Department of Chest Diseases, University of Health Sciences, Süreyyapaşa Training and Research Hospital, Istanbul, Turkey

Adv Dermatol Allergol 2024; XLI (4): 400–407
DOI: https://doi.org/10.5114/ada.2024.142187

## Abstract

**Introduction:** Tuberculosis is a communicable illness and one of the leading causes of death, especially in developing countries like Turkey. One of the problems that must be managed well in the treatment of tuberculosis is drug hypersensitivity. The first-line agents are very important for the success of treatment. Alternative drugs are more toxic and less successful in treatment. Therefore, it is very important to be able to include first-line drugs in the post-hypersensitivity regimen. At this point, the success of desensitization comes to the fore. There are fewer studies on rapid drug desensitization in delayed-type drug hypersensitivity to anti-tuberculosis drugs.

**Aim:** The primary aim of the study was to determine the prevalence of delayed-type hypersensitivity reactions in drug-sensitive cases; the secondary aim was to determine the appropriate treatment management.

**Material and methods:** This was a retrospective study. Demographic features, tuberculosis diagnostic indicator, clinical signs of developing a hypersensitivity reaction, reaction time, desensitization scheme and treatment were evaluated.

**Results:** A total of 41 tuberculosis cases were included in the study. Twenty-six of the cases were male; mean age (mean ± SD) 55.44 ±16.93 years; 70.7% of them were diagnosed bacteriologically; 70.7% of them were diagnosed with pulmonary tuberculosis. The most common skin finding was maculopapular drug eruption. The development time (mean ± SD) of the reaction in patients who developed a reaction was 34.93 ±39.62 days. The responsible agent could be identified in 15 reactions. The most common drug responsible for the reaction was rifampicin. Successful desensitization was achieved in 19 (46.3%) cases with the sensitive regimen. The duration of treatment was 8.97 ±3.44 months. When evaluated in terms of treatment results, cure and treatment completion were accepted as treatment success. In this case, 30 (73.2%) patients successfully completed the treatment.

**Conclusions:** Our study is one of the largest series in which delayed-type hypersensitivity develops under tuberculosis treatment and the desensitization scheme is recommended. A practical, easy desensitization scheme had been shared in this paper.

**Key words:** tuberculosis, delayed-type drug hypersensitivity, rifampicin, maculopapular eruption.

## Introduction

Tuberculosis is a communicable illness and one of the leading causes of death, especially in developing countries like Turkey [1]. One of the problems that must be managed well in the treatment of tuberculosis is drug hypersensitivity [2]. The prevalence of hypersensitivity to tuberculosis drugs was 7.8% in a study conducted with patients hospitalized in a tertiary healthcare institution in Turkey. Among these reactions, delayed drug hypersensitivity was the most common [3]. When we say delayed-type hypersensitivity, we mean maculopapular eruption, fixed drug eruption, acute generalized eczematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and lichenoid drug eruption [4]. Type IV or delayed-type hypersensitivity reactions are mediated by T cells and cytokines and can occur at any time 24 h after ingestion [5]. Treatment is interrupted when hypersensitivity develops in anti-tuberculosis therapy. Hypersensitivity is treated, then a new regimen is established after therapeutic tests are started. The first-line agents (isoniazid, rifampicin, ethambutol, pyrazinamide) are very important for the success of treatment. Alternative drugs are more toxic and less successful in treatment [6]. Therefore, it is very important to be able to include first-line drugs in the

**Address for correspondence:** Zeynep Yegin Katran, Department of Allergy and Immunology, University of Health Sciences, Süreyyapaşa Training and Research Hospital, Altay Çeşme Street, Efe Boz House No: 3/12 Maltepe, Istanbul, Turkey, phone: +90 0505 255 56 25, e-mail: zynpyegin@hotmail.com

**Received:** 2.05.2024, **accepted:** 31.05.2024, **online publication:** 12.08.2024.

post-hypersensitivity regimen. At this point, the success of desensitization comes to the fore. Studies on drug desensitization in delayed-type hypersensitivity are less common than in early-type hypersensitivity [4].

There are defined rapid drug desensitization schemes in delayed-type drug hypersensitivity with different antibiotic groups such as β-lactam antibiotics, sulfonamide, co-trimoxazole, chemotherapy and monoclonal antibodies [7–9]. There are fewer studies on rapid drug desensitization in delayed-type drug hypersensitivity to anti-tuberculosis drugs [6]. The mechanism of action of rapid drug desensitization in delayed-type drug hypersensitivity is not clear. However, basophil and mast cell are thought to suppress T cell activity [10].

In this study, the characteristics of the patients with delayed-type drug hypersensitivity developed while being treated for tuberculosis, the desensitization scheme applied and the treatment success were evaluated.

## Aim

The primary aim of the study was to determine the prevalence of delayed-type hypersensitivity reactions in drug-sensitive cases; the secondary aim was to determine the appropriate treatment management.

## Material and methods

The design of the study was a retrospective study and patients hospitalized in the Tuberculosis department of our hospital between 1.02.2015 and 1.05.2021 were included. Patients aged 18 years and older who developed delayed-type hypersensitivity to antituberculosis drugs and were consulted at the Allergy and Immunology department were examined.

All of the patients were inpatients and the hypersensitivity reactions that developed after drug treatment were confirmed by Allergy and Immunology specialists. Patients who did not receive desensitization in accordance with the scheme and patients with non-tuberculosis mycobacterial infections were not included.

Demographic data of the patients, diagnosis of tuberculosis, clinical features of type 4 immediate hypersensitivity reaction and time of occurrence, drug treatments, and treatment results were evaluated. Age, gender and nationality were noted in demographic data. Tuberculosis diagnoses, organ involvement and treatments were evaluated as determined in the Turkish Ministry of Health Tuberculosis Diagnosis and Treatment Guideline published in 2019. Diagnoses were classified as smear positive, culture positive, molecular test positive, histopathological diagnosis, clinical radiological diagnosis; organs affected by tuberculosis were classified as pulmonary and extrapulmonary; the extrapulmonary group was classified as miliary, lymph node, pleura, kidney, pericardium and larynx [11].

Hypersensitivity reactions were evaluated as defined in the 2019 Approach to Drug Hypersensitivity Reactions: National Guideline Update. Type 4 hypersensitivity reactions, maculopapular eruption, fixed drug eruption, SJS, TEN, AGEP, erythema multiforme, lichenoid drug eruption that developed 6 h or later after taking the drug were evaluated [12]. After the treatment of type 4 hypersensitivity reactions in all patients included in the study, drug desensitization was performed in their stable period.

The development time of the current reaction, the success of the applied desensitization, and the duration of treatment were evaluated. In our desensitization, patients who developed a reaction, isoniazid, rifampicin, ethambutol and finally streptomycin/pyrazinamide were added respectively. If alternative drugs were to be given, isoniazid, rifampicin, ethambutol and streptomycin/pyrazinamide were given first. Other alternative drugs were then given in a non-standard order.

The intradermal test and patch test are the recommended diagnostic approach for those who develop type 4 hypersensitivity reactions [3]. If patients underwent this diagnostic testing process, it was noted.

If an allergic reaction did not develop after each drug was given with desensitization in those who developed a type 4 hypersensitivity reaction, the drug was given with desensitization after the full dose was given for 7 days. Drug doses in desensitization were made as suggested by Buhari *et al.* [13]. However, unlike what was stated in the protocol, pyrazinamide was given as the last one during the administration of the drugs. When a drug hypersensitivity reaction developed, after the reaction was treated in accordance with international guidelines, the patient was re-evaluated and desensitized. After the regimen was completed, the patient was given the full dose of the regimen in one go in the morning for several days (Table 1).

### Statistical analysis

In the statistics of the study, all analyses were performed using SPSS 22.0. Differences in the means were evaluated with the Mann-Whitney *U* test. Relative risk, odd ratios, and 95% confidence intervals were calculated. $\chi^2$ and logistic regression analysis were used for categorical parameters.

## Results

During the study, 2677 patients were hospitalized in the Tuberculosis inpatient department; delayed-type hypersensitivity reaction was seen in 53 patients. The prevalence of delayed-type hypersensitivity in hospitalized patients was 1.9%. Forty-one patients whose drug desensitization was performed in accordance with the scheme were included. Twenty-six (63.4%) of the cases were male. Mean age (mean ± SD) (min.–max.) was 55.44 ±16.93 (18–87) years; 40 (97.6%) of them were citizens

**Table 1.** Desensitization scheme for delayed-type hypersensitivity

| Desensitization scheme applied in patients with type 4 delayed drug hypersensitivity reaction | | |
|---|---|---|
| Day 1 | 8:00: Isoniazid | |
| | Solution A: 1 tablet of 300 mg of isoniazid is diluted with 40 $cm^3$ of 0.9% NaCl | |
| | The resulting concentration is 7.5 mg/ml | |
| | 8:00 1 $cm^3$ of solution A | 7.5 mg |
| | 8:30 2 $cm^3$ of solution A | 15 mg |
| | 9:00 3 $cm^3$ of solution A | 22.5 mg |
| | 9:30 1/8 tablet of isoniazid | 37.5 mg |
| | 10:00 ¼ tablet of isoniazid | 75 mg |
| | 11:00 ½ tablet of isoniazid | 150 mg |
| Day 2–7 | 8.00: Isoniazid 300 mg | |
| Day 8<br>300 mg of isoniazid | 9.00: For rifampicin | |
| | Solution B: 2 capsules of 600 mg of rifampicin are diluted with 60 $cm^3$ of 0.9% NaCl. The resulting concentration is 10 mg/ml | |
| | 8:00 1 $cm^3$ of solution B | 10 mg |
| | 8:30 2 $cm^3$ of solution | B 20 mg |
| | 9:00 5 $cm^3$ of solution B | 50 mg |
| | 9:30 10 $cm^3$ of solution B | 100 mg |
| | 10:00 20 $cm^3$ of solution B | 200 mg |
| | 11:00 22 $cm^3$ of solution B | 220 mg |
| Day 9–14 | Isoniazid 300 mg + rifampicin 600 mg | |
| Day 15<br>8.00: Isoniazid 300 mg + rifampicin 600 m | 9.00: For ethambutol | |
| | Solution C: 1 tablet of 500 mg ethambutol is diluted with 10 $cm^3$ of 0.9% NaCl. The resulting concentration is 50 mg/ml | |
| | Solution D: It is taken from 2 $cm^3$ of solution C. It is diluted with 18 cm3 of 0.9% NaCl. The resulting concentration is 5 mg/ml | 5 mg |
| | 8:00 1 $cm^3$ of solution D | 10 mg |
| | 8:30 2 $cm^3$ of solution D | 10 mg |
| | 9:00 4 $cm^3$ of solution D | 20 mg |
| | 9:30 8 $cm^3$ of solution D | 40 mg |
| | 10:00 2 $cm^3$ of solution C | 100 mg |
| | 10:30 4 $cm^3$ of solution C | 200 mg |
| | 11:00 One tablet of ethambutol | 500 mg |
| | 12:00 1¼ tablet of ethambutol | 625 mg |
| Day 16–21 | 8.00: Isoniazid 300 mg + rifampicin 600 mg + ethambutol 1500 mg | |
| Day 22<br>8.00: Isoniazid 300 mg + rifampicin 600 mg + ethambutol 1500 mg | 9.00: For pyrazinamide | |
| | Solution E: 1 tablet of 500 mg pyrazinamide is diluted with 10 $cm^3$ of 0.9% NaCl. The resulting concentration is 50 mg/ml | |
| | Solution F: It is taken from 3 $cm^3$ of solution E. It is diluted with 27 $cm^3$ of 0.9% NaCl. The resulting concentration is 5 mg/ml | |
| | 8:00 2 $cm^3$ of solution F | 10 mg |
| | 8:30 4 $cm^3$ of solution F | 20 mg |
| | 9:00 8 $cm^3$ of solution F | 40 mg |
| | 9:30 16 $cm^3$ of solution F | 80 mg |
| | 10:00 3 $cm^3$ of solution E 150 mg | 150 mg |
| | 10:30 4 $cm^3$ of solution E 200 mg | 200 mg |
| | 11:00 One tablet of pyrazinamide | 500 mg |
| | 12:00 2 tablets of pyrazinamide | 1000 mg |
| Day 23: 8.00 HRZE | | |
| Day 24: 8.00 HRZE | | |
| Day 25: 8.00 HRZE | | |

**Drug doses in desensitization were made as suggested by Buhari et al. [14].*

of the Republic of Turkey; 29 (70.7%) of them were diagnosed bacteriologically; 29 (70.7%) of them were diagnosed with pulmonary tuberculosis; 2 (4.8%) of them had previously received antituberculosis treatment. Antituberculosis therapy (isoniazid, rifampicin, ethambutol, pyrazinamide) was initiated in all cases with drug sensitivity (Table 2).

The most common skin finding was maculopapular drug eruption, which was seen in 26 (63%) cases. Lichenoid drug eruption was observed in 9 (21.6%) cases, ery-

**Table 2.** Demographic and clinical characteristics of the patients

| Variable | | | *N* (%) |
|---|---|---|---|
| Gender | Female | | 15 (36.6) |
| | Male | | 26 (63.4) |
| Age | Mean ± SD<br>Min.–max. | | 55.44 ±16.93<br>(18-87) |
| Nationality | Turkey | | 40 (97.6) |
| | Pakistan | | 1 (2.4) |
| Who country classification | | Asia | 41 (100) |
| Diagnosis | | Sputum positive | 23 (56.1) |
| | | Culture positive | 6 (14.6) |
| | | Molecular test positive | 3 (7.3) |
| | | Histopathological | 7 (17.1) |
| | | Clinical-radiological | 2 (4.9) |
| Organ affected by tuberculosis | Pulmonary | | 34 (82.9) |
| | Extrapulmonary | Lymph node | 6 (14.6) |
| | | Pleura | 1 (2.4) |
| Prior treatment | No | | 39 (95.1) |
| | Yes | Recurrence | 1 (2.4) |
| | | Patient out of folow up | 1 (2.4) |

thema multiforme in 2 (4.8%) cases, DRESS in 1 (2.4%) case, and fixed drug eruption in 2 (4.8%) cases. SJS and TEN were not observed (Table 3). The development time (mean ± SD) of the reaction in patients was 34.93 ±39.62 days. The time between index reaction and reintroduction of treatment was 41.3 ±20.4 days.

When hypersensitivity developed, it was sufficient to discontinue the current treatment regimen in 11 (26.8%) patients. Oral/parenteral steroids were given to 16 (39%) patients (Table 4).

The responsible agent could be identified in 15 reactions. The most common drug responsible for the reaction was rifampicin in 7 patients. Rifampicin was followed by pyrazinamide and isoniazid. Multiple drug hypersensitivity (moxifloxacin and rifampicin) was detected in only one case. A 25-year-old woman was diagnosed with pulmonary tuberculosis. Initial treatment was HRZE (isoniazid, rifampicin, ethambutol, pyrazinamide). Lichenoid drug eruption developed after treatment. Desensitisation was initially performed to isoniazid, ethambutol, moxifloxacin and rifampicin. Hypersensitivity developed after both moxifloxacin and rifampicin. The patient was considered allergic to these two agents. Treatment was completed with protionamide, cycloserine, para amino salicylic acid and levofloxacin.

**Table 3.** Clinical features of hypersensitivity developed to tuberculosis treatment

| Hypersensitivity reactions | Female *N* (%) | Male *N* (%) | Total *N* (%) |
|---|---|---|---|
| Maculopapular drug eruption (MPE) | 9 (21.6) | 17 (41.4) | 26 (63) |
| Erythema multiforme | 1 (2.4) | 1 (2.4) | 2 (4.8) |
| Lichenoid drug eruption | 3 (7.2) | 6 (14.4) | 9 (21.6) |
| Fixed drug eruption | – | 2 (4.8) | 2 (4.8) |
| Drug rash with eosinophilia and systemic symptoms (DRESS)* | 1 (2.4) | – | 1 (2.4) |
| Exfoliative dermatitis | – | 1 (2.4) | 1 (2.4) |

**(65y, F. In pulmonary tuberculosis, isoniazid, rifampicin, ethambutol, pyrazinamide treatment was started. She was diagnosed with DRESS on the 60th day of treatment. Her treatment was discontinued. The patient's treatment compliance was very difficult and she wanted to leave the treatment all the time. The patient was being treated with moxifloxacin, cycloserine, linezolid and protionamide. Each drug was started one by one with desensitization. The treatment was completed in 10 months without any allergic reaction.).*

**Table 4.** Drugs responsible for hypersensitivity

| Responsible drug | Female | Male | Total |
|---|---|---|---|
| Isoniazid | 2 | – | 2 |
| Rifampicin | 3 | 4 | 7 |
| Ethambutol | – | – | – |
| Pyrazinamide | 1 | 3 | 4 |
| Streptomycin | – | – | – |
| Levofloxacin | – | – | – |
| Moxifloxacin | 1 | | 1 |
| Capreomycin | – | – | – |
| Amikacin | – | – | – |
| Para amino salicylic acid | – | – | – |
| Protionamide | – | – | – |
| Cycloserine | – | 1 | 1 |
| Linezolid | – | – | – |
| Total | 7 | 8 | 15 |

In delayed-type hypersensitivity, intradermal test and patch test were recommended to find the responsible drug [3]. In 5 cases, intradermal test early and late readings were made with rifampicin at a concentration of 1/30000 and no positivity was observed. Patch testing was performed in 6 cases. We did not have any patients who underwent *in vitro* testing before reintroduction. The characteristics of the patients who underwent intradermal test and patch test are as indicated in Table 5. In Table 5, patient number 5 was examined in detail. A 33-year-old female patient was started on isoniazid, rifampicin, ethambutol, and pyrazinamide due to pulmonary tuberculosis. When maculopapular rash developed after 1 week, the treatment was discontinued and she

**Table 5.** The characteristics of the patients who underwent intradermal test and patch test

| No. | Organ involvement, hypersensitivity reaction | Intradermal test Result | Patch test Result | Initial treatment | Final treatment regimen | Hypersensitivity responsible agent |
|---|---|---|---|---|---|---|
| 1 | Pulmonary, lichenoid drug eruption | Rifampicin Negative | HRZE Negative | HRZE | HRZE | Not determined |
| 2 | Pulmonary, lichenoid drug eruption | Levofloxacin Negative | Amikacin Protionamide Isoniazid PAS Levofloxacin Cycloserine Positive | | Amikacin Protionamide Isoniazid PAS Levofloxacin Cycloserine | Cycloserine |
| 3 | Pleura MPE | Rifampicin Negative | HRZE Negative | | HRZE | Not determined |
| 4* | Lymph node MPE | Rifampicin Negative | HRZE Negative | | Isoniazid Ethambutol Pyrazinamide Moxifloxacin Cycloserine | Not determined |
| 5 | Pulmonary MPE | Rifampicin Negative | HRZE Positive** | | Isoniazid Ethambutol Pyrazinamide Moxifloxacin Cycloserine Amikacin | Rifampicin |
| 6 | Lymph node MPE | Rifampicin Negative | HRZE Negative | | Isoniazid Ethambutol Pyrazinamide Moxifloxacin Cycloserine Amikacin | Rifampicin*** |

**Rifampicin was withdrawn from the regimen due to interstitial nephritis. **Rifampicin was excluded from the regimen due to positive patch test. ***Rifampicin was excluded from the regimen because itching and urticaria plaques developed in the neck region after desensitization. PAS – Para amino salicylic acid, HRZE – isoniazid, rifampicin, ethambutol, pyrazinamide.*

was hospitalized. Prick testing was performed with isoniazid, rifampicin, ethambutol and pyrazinamide and was found to be negative. Intradermal test was done with rifampicin ampoule and it was found negative. Patch tests of isoniazid, rifampicin, ethambutol and pyrazinamide were performed. It was removed from the regimen only when the patch test was positive with rifampicin at the 48$^{th}$ h. Tuberculosis doctors identified the new regimen as isoniazid, ethambutol, pyrazinamide, moxifloxacin, cycloserine, and amikacin. The patient completed the tuberculosis treatment without the development of hypersensitivity.

Although desensitization was initiated with the sensitive regimen in all cases, successful desensitization was achieved in 19 (46.3%) cases. In 3 (7.3%) cases, the regimen was changed due to hepatotoxicity. In 19 (46.3%) cases, it was necessary to change the regimen due to the development of hypersensitivity after the first desensitization, and success was achieved with the changed regimen. In desensitization, drugs were given in accordance with the recommended scheme. If alternative drugs were also planned to be started, first-line drugs were started first, then other drugs were added.

The duration of treatment was 8.97 ±3.44 months (6–18 months). When evaluated in terms of treatment results, cure and treatment completion were accepted as treatment success. In this case, 30 (73.2%) patients successfully completed the treatment: 1 (2.4%) patient was excluded from follow-up, 1 (2.4%) had treatment failure, 1 (2.4%) patient died during the treatment process, 8 (19.5%) patients are still under treatment.

## Discussion

In this study, patients who developed delayed-type hypersensitivity to tuberculosis treatment were treated as inpatients. When completing tuberculosis treatment after desensitization was accepted as treatment success; the scheme was successful in 30 (73.2%) patients. Severe reactions such as SJS or TEN were not observed. The most common hypersensitivity was maculopapular eruption and the most common responsible agent was rifampicin.

The prevalence of delayed-type hypersensitivity in hospitalized patients was 1.9% in our study. In a study examining patients who developed DRESS through the hospital registry system, the prevalence was 1.2% [13].

We think that the prevalence was higher, because all patients with delayed-type hypersensitivity were included in our study (not only DRESS) [14].

In this study, the mean age of our patients was 55.44 ±16.93 (18–87) years. In the study of Oh *et al*., the mean age of the patients was 55 years [15]. The mean age was found to be similar in the study in which delayed-type severe drug reactions were evaluated in Korea [15].

In the study conducted in Australia, 45% [6] of the patients, and in the Korean study, 47% [15] of the patients were male. In our study, 63.4% of the patients were male. Adverse drug reactions are more common in females [16]. In a few publications, it is mentioned that the male gender is at the forefront [17, 18]. These data were found to be inconsistent with the literature. We think that more comprehensive studies to be conducted on the Asian race will clarify the subject.

The frequency of reactions was higher in patients with bacteriological tuberculosis and pulmonary tuberculosis. There are studies supporting that severe delayed-type drug hypersensitivity reactions are more common in patients with pulmonary tuberculosis [6, 14].

The development time (mean ± SD) of the reaction in patients who developed a reaction was 34.93 ±39.62 days. While there are studies indicating that the hypersensitivity reaction occurs earlier [5, 13], there are also studies showing that it occurs later [19]. In general, we can say that such reactions are seen after the 4$^{th}$ week of anti-tuberculosis treatment. It is important to keep this in mind in the treatment follow-up of the patients.

In this study, the most common hypersensitivity reactions were maculopapular and lichenoid drug eruption. Severe-type reactions such as SJS or TEN were not seen. In other studies, the most common type of hypersensitivity reactions was maculopapular eruption [19, 20].

Diagnostic tests recommended in delayed-type hypersensitivity are patch test and delayed control of intradermal test [4]. The situation is the same in tuberculosis [21, 22]. According to Zaiem *et al*., patch test positivity rates are low in DRESS. However, if the patch test is positive, it provides the advantage of removing the drug from the regimen [23, 24]. Our study is retrospective and patch tests were evaluated according to patient files. Patch testing was performed in 6 patients and was positive in 2 patients. In one of the 2 patients, the drug was removed from the regimen. In one, desensitization was applied.

When hypersensitivity develops during the tuberculosis treatment process, 3 different pathways can be followed. In the first one, especially if the reaction is severe such as SJS or TEN, all drugs can be changed. In the second one, the regimen can be changed by performing diagnostic tests (patch, intradermal test). In the third one, the same drugs can be used again with desensitization [14]. In this study, if the hypersensitivity was maculopapular eruption, fixed drug eruption or lichenoid drug eruption, drugs were given by desensitization. However, if the hypersensitivity was DRESS, SJS, TEN, erythema multiforme, the whole regimen was changed. All changed drugs were started with desensitization.

In our study, each drug was given by rapid desensitization. When each drug was added, patients waited 7 days for new drugs. Ban *et al.* also used 3-day intervals for each drug addition [6].

In other studies, the target total dose was reached in 3 days [14, 24, 25]. There are also studies suggesting starting each drug in 14 days with slow desensitization [12]. Horne and Grant noticed that isoniazid resistance developed on days 16 and 23 when performing drug desensitization in 2 patients diagnosed with pulmonary tuberculosis in 1963 [26]. Delay in the treatment of tuberculosis both increases the transmission of the disease and causes the development of resistance. These both increase the cost of treatment and impair patient compliance [6, 11]. In our study, all of the patients were hospitalized in the tuberculosis department under the supervision of a doctor, possible allergic complaints could be checked daily. Due to the advantage of not delaying the treatment and catching the reaction that might develop early, the drugs were given at 7-day intervals.

No drug therapy was used for premedication before desensitization. Ban *et al*. gave antihistamines to patients before desensitization [6]. Moreover, it was observed that the use of antihistamines and steroids before desensitization did not increase the success of desensitization [19]. We think that it would be more accurate to evaluate the success of desensitization without the use of antihistamine treatment.

In a series of patients diagnosed with DRESS, the most common responsible agent was rifampicin [14]. In two other studies including patients who developed drug-induced maculopapular eruption, ethambutol was found to be the most common responsible agent [13, 26]. As in the literature, in our study the most common responsible agent was rifampicin.

When delayed-type hypersensitivity develops in tuberculosis, it may be necessary to interrupt the treatment and give steroids. This situation both makes the disease disseminated and causes drug resistance [27]. Several authors have suggested starting steroid treatment [28]. This issue is controversial and prospective studies with large series are needed.

When completing tuberculosis treatment after desensitization was accepted as treatment success; the scheme was successful in 30 (73.2%) patients. In this study we did not have severe allergic reactions. In another study, the desensitization success rate was 80.7%. It was mentioned that the desensitization success was not related with kinds of anti-tuberculosis medication and clinical manifestation of drug hypersensitivity [6].

This study has some limitations as it is a single-centre and retrospective study. Intradermal test and patch

test were not performed in all patients. These limitations should be considered carefully.

Our study is one of the largest series of patients who developed delayed-type hypersensitivity while being treated for tuberculosis and the desensitization scheme is recommended. A practical, easy desensitization scheme had been shared in this paper.

## Acknowledgments

We would like to thank all our fellow and nurse team that we work together.

## Funding

No external funding.

## Ethical approval

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 01.12.2022, protocol code: 116.2017.R-263). Written informed consent to participate and publish was obtained from all individual participants included in the study.

## Conflict of interest

The authors declare no conflict of interest.

### References

1. Jeremiah C, Petersen E, Nantanda R, et al. The WHO Global Tuberculosis 2021 Report – not so good news and turning the tide back to end TB. Int J Infect Dis 2022; 124: S26-9.
2. Tan WC, Ong CK, Kang SC, Razak MA. Two years review of cutaneous adverse drug reaction from first line anti-tuberculous drugs. Med J Malaysia 2007; 62: 143-6.
3. Katran ZY, Bulut I, Babalik A, Keren M. Treatment and management of hypersensitivity reactions developed against anti-tuberculosis drug. Int J Mycobacteriol 2022; 11: 309-17.
4. Scherer K, Brockow K, Aberer W, et al.; ENDA, the European Network on Drug Allergy and the EAACI Drug Allergy Interest Group. Desensitization in delayed drug hypersensitivity reactions -- an EAACI position paper of the Drug Allergy Interest Group. Allergy 2013; 68: 844-52.
5. Mayorga C, Celik G, Rouzaire P, et al.; In vitro tests for Drug Allergy Task Force of EAACI Drug Interest Group. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2016; 71: 1103-34.
6. Ban GY, Jeong YJ, Lee SH, et al. Efficacy and tolerability of desensitization in the treatment of delayed drug hypersensitivities to anti-tuberculosis medications. Respir Med 2019; 147: 44-50.
7. McNulty CMG, Park MA. Delayed cutaneous hypersensitivity reactions to antibiotics: management with desensitization. Immunol Allergy Clin North Am 2017; 37: 751-60.
8. Whitaker P, Shaw N, Gooi J, et al. Rapid desensitization for non-immediate reactions in patients with cystic fibrosis. J Cyst Fibros 2011; 10: 282-5.
9. Vega A, Peña MI, Torrado I. Use of rapid drug desensitization in delayed hypersensitivity reactions to chemotherapy and monoclonal antibodies. Front Allergy 2022; 2: 786863.
10. Castells MC. A new era for drug desensitizations. J Allergy Clin Immunol Pract 2015; 3: 639-40.
11. Republic of Turkey Ministry of Health, Tuberculosis Diagnosis and Treatment Guide, 2nd Edition (Ankara, 2019). Available from: https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz_db/haberler/Tuberkuloz_Tani_Ve_Tedavi_Rehberi_/Tuberkuloz_Tani_ve_Tedavi_Rehberi.pdf. [Last accessed on 2022 Sep 02].
12. Çelik GE, Dursun AB. Turkish National Society of Allergy and Clinical Immunology, Approach to Drug Hypersensitivity Reactions: National Guideline Update; 2019. Available from: https://www.aid.org.tr/wp-content/uploads/2019/12/%C4%B0la%C3%A7-Rehberi-2019-SON.pdf. [Last accessed on 2022 Sep 02].
13. Buhari GK, Keren M, Dursun AB, et al. Immediate-type hypersensitivity reactions due to antituberculosis drugs: a successful readministration protocol. Ann Allergy Asthma Immunol 2015; 115: 39-44.
14. Jung HY, Park S, Shin B, et al. Prevalence and clinical features of drug reactions with eosinophilia and systemic symptoms syndrome caused by antituberculosis drugs: a retrospective cohort study. Allergy Asthma Immunol Res 2019; 11: 90-103.
15. Oh JH, Yun J, Yang MS, et al. Reintroduction of antituberculous drugs in patients with antituberculous drug-related drug reaction with eosinophilia and systemic symptoms. J Allergy Clin Immunol Pract 2021; 9: 3442-9.e3.
16. Jin HJ, Kang DY, Nam YH, et al; Korean Severe Cutaneous Adverse Reactions Consortium (KoSCAR). Severe cutaneous adverse reactions to anti-tuberculosis drugs in Korean patients. Allergy Asthma Immunol Res 2021; 13: 245-55.
17. Blumberg HM, Burman WJ, Chaisson RE, et al.; American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003; 167: 603-62.
18. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents a 6 year series from Chandigarh, India. J Postgrad Med 2001; 47: 95-9.
19. Patel RM, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol 2008; 74: 430.
20. Siripassorn K, Ruxrungtham K, Manosuthi W. Successful drug desensitization in patients with delayed-type allergic reactions to anti-tuberculosis drugs. Int J Infect Dis 2018; 68: 61-8.
21. Shin HJ, Chang JS, Kim MS, et al. Hypersensitivity reactions to multiple anti-tuberculosis drugs. PLoS One 2021; 16: e0246291.
22. Arruti N, Villarreal O, Bernedo N, et al. Positive Allergy Study (Intradermal, Patch, and Lymphocyte Transformation Tests) in a case of isoniazid-induced DRESS. J Investig Allergol Clin Immunol 2016; 26: 119-20.
23. Lehloenya RJ, Todd G, Wallace J, et al. Diagnostic patch testing following tuberculosis-associated cutaneous adverse drug reactions induces systemic reactions in HIV-infected persons. Br J Dermatol 2016; 175: 150-6.
24. Zaiem A, Toujani S, Hamza I, et al. DRESS associé aux antituberculeux avec test épicutané positif a` l'isoniazide Rev fr allergol 2013; 53: 361-71.

25. Ingen-Housz-Oro S, Assier H, Gener G, et al.; Groupe FISARD de la SFD. Hypersensibilité retardée aux traitements antituberculeux. Proposition d'une conduite à tenir pratique devant un exanthème : quand arręter, quelles explorations allergologiques et comment réintroduire le traitement [Delayed hypersensitivity to anti-tuberculosis drugs. Proposed practical management plan for exanthema: when to stop, which allergological investigations to perform, and how to restart treatment]. Ann Dermatol Venereol 2019; 146: 313-8.
26. Horne NW, Grant IW. Development of drug resistance to isoniazid during desensitization: a report of two cases. Tubercle 1963; 44: 180-2.
27. Sim DW, You HS, Yu JE, Koh YI. High occurrence of simultaneous multiple-drug hypersensitivity syndrome induced by first-line anti-tuberculosis drugs. World Allergy Organ J 2021; 14 :100562.
28. Sharma RK, Verma GK, Tegta GR, et al. Spectrum of cutaneous adverse drug reactions to anti-tubercular drugs and safe therapy after re-challenge – a retrospective study. Indian Dermatol Online J 2020; 11: 177-81.