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Reintroduction of antituberculous drugs in patients with antituberculous drug related drug reaction with eosinophilia and systemic symptoms

Ji Hyun Oh, MD, James Yun, MD, PhD, Min-Suk Yang, MD, PhD, Jung-Hyun Kim, MD, Sae-Hoon Kim, MD, PhD, Sujeong Kim, MD, Jeong-Hee Choi, MD, PhD, Jae-Joon Yim, MD, PhD, Hye-Ryun Kang, MD, PhD

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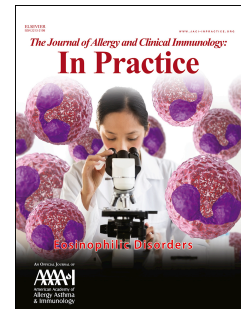
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drug reaction with eosinophilia and systemic symptoms**

Ji Hyun Oh MD^{1,2}, James Yun MD, PhD^{3,4}, Min-Suk Yang MD, PhD⁵, Jung-Hyun Kim MD⁶,
Sae-Hoon Kim MD, PhD⁶, Sujeong Kim MD⁷, Jeong-Hee Choi MD, PhD⁸, Jae-Joon Yim
MD, PhD⁹, Hye-Ryun Kang MD, PhD^{1,9,10}

¹Institute of Allergy and Clinical Immunology, Seoul National University Medical Research
Center, Seoul National University College of Medicine, Seoul, Korea

²Division of Respiratory-Allergy Medicine, Department of Internal Medicine,
Soonchunhyang University College of Medicine, Cheonan, Korea

³Department of Immunology and Rheumatology, Nepean Hospital, Sydney, Australia

⁴The University of Sydney, Sydney, Australia

⁵Department of Internal Medicine, Seoul Metropolitan Government Seoul National
University Boramae Medical Center, Seoul, Korea

⁶Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam,
Korea.

⁷Department of Internal Medicine, School of Medicine, Kyungpook National University,
Daegu, Korea

⁸Department of Pulmonology and Allergy, Hallym University Dongtan Sacred Heart Hospital,
Hwaseong, Korea

⁹Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul
National University College of Medicine, Seoul, Korea

¹⁰Drug Safety Monitoring Center, Seoul National University Hospital, Seoul, Korea

Running title: Desensitization in patients with DRESS to antituberculous drug

Correspondence: Hye-Ryun Kang, MD, PhD

Department of Internal Medicine, Seoul National University College of Medicine

101 Daehak-ro, Jongno-gu, Seoul, Korea.

Fax: 82-2-764-2199, Telephone: 82-2-2072-0820, E-mail: helenmed@snu.ac.kr

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Highlights box**What is already known about this topic?**

Antituberculous drug-induced drug reaction with eosinophilia and systemic symptom (DRESS) usually appear as multi-drug hypersensitivity reactions resulting in limited antituberculous drug choices at resuming antituberculous treatment and increased treatment interruption.

What does this article add to our knowledge?

Resuming anti-TB medication based on desensitization protocols may be a safe and effective option for those with antituberculous drug-related DRESS compared to changing all the drugs and graded challenge method.

How does this study impact current management guidelines?

Desensitization protocol to resume antituberculous medication in DRESS patients might contribute to the control of tuberculosis by enabling effective and safe antituberculous treatment if it can be appropriately performed and closely monitored.

Abstract

Background: Patients who suffered drug reaction with eosinophilia and systemic symptom (DRESS) during the treatment of tuberculosis (TB) commonly experience multi-drug hypersensitivity reactions resulting in limited anti-TB drug choices. Therefore, reintroduction based on desensitization protocol may be an option to resume anti-TB medication.

Objective: To evaluate the outcomes and safety of resuming anti-TB drugs according to reintroduction methods in patients with anti-TB drug-related DRESS.

Methods: A retrospective cohort of patients who had experienced anti-TB drug-related SCARs from 2011 to 2017 was established from separate five institutions.

Results: Anti-TB medication was resumed in 27 out of 29 patients with anti-TB drug-related DRESS through complete changing regimen (n=9), reintroduction by graded challenge (n=5), or reintroduction using desensitization protocol (n=13). Nine patients completely changed their anti-TB regimen to second-line TB drugs but only one (11.1%) succeeded in maintaining new anti-TB drugs. The other eight failed to take drugs due to the occurrence of hypersensitivity reactions to the newly introduced anti-TB drugs. Two (40.0%) of five patients who underwent graded rechallenges successfully completed anti-TB drugs while three (60%) failed to resume anti-TB drugs due to the recurrence of hypersensitivity reactions. In 13 patients who resumed anti-TB drugs using desensitization protocol, no one who underwent desensitization developed recurrence of DRESS; 11 (84.6%) eventually completed anti-TB treatment and two eventually failed to complete anti-TB treatment due to late onset itching and drug induced liver injury.

Conclusions: Resuming anti-TB medication based on desensitization protocols may be a safe and effective option for those with anti-TB drug-related DRESS.

81 **Keywords:** Antitubercular Agents; Drug Hypersensitivity; Drug Hypersensitivity Syndrome;
82 Immunologic Desensitization

83 **Abbreviations**

84 TB: Tuberculosis

85 SCARs: Severe cutaneous adverse reactions

86 DRESS: Drug reaction with eosinophilia and systemic symptoms

87 SJS: Stevens–Johnson syndrome

88 TEN: Toxic epidermal necrolysis

89 BTR: Breakthrough reactions

90 DILI: Drug-induced liver injury

Introduction

Tuberculosis (TB), one of the leading causes of death from a single infectious disease, is still a significant threat to human health and the number of affected patients reached 10.0 million in 2017.¹ The anti-TB treatment takes 6–9 months and sometimes longer; therefore, adherence to treatment is critical for cure. Drug hypersensitivity reactions or adverse reactions to anti-TB drugs are the leading cause of drug changes or discontinuation.

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), are rare but potentially life-threatening delayed drug hypersensitivity reactions. The mortality rates associated with DRESS, SJS, and TEN are estimated at up to 10%, 5–10%, and 25–38%, respectively.^{2, 3} Once SCARs are diagnosed, culprit drug(s) should be discontinued promptly, and reintroduction of the culprit drugs is contraindicated due to the risk of SCAR recurrence.

However, in cases of SCARs related to anti-TB drugs, anti-TB drugs need to be resumed for the treatment of underlying TB infection. Although the reintroduction of the first-line anti-TB drugs is ideal, it is difficult to choose safe anti-TB drugs because the culprit drug(s) cannot be easily determined due to simultaneous administration of multiple drugs at the time of the index reaction. Avoiding all the drugs administered to patients with SCARs is generally recommended for the fear of recurrence, but drug hypersensitivity reactions are still frequently observed even after changing all the drugs previously administered, particularly in DRESS cases. This characteristic feature of multiple drug hypersensitivity in anti-TB drug-related DRESS makes it more difficult to resume anti-TB medications, and currently there is no standardized recommendation for the resumption of anti-TB drugs in these patients.

Desensitization is a stepwise administration of allergen starting from a subthreshold dose to full therapeutic dose to induce tolerance. Sometimes, a similar desensitization protocol can

be applied to reduce the risk of sensitization to drugs with allergenic potential in high-risk patients in ‘tolerance induction’.^{4, 5} Therefore, adopting a desensitization protocol may be a reasonable option for patients with anti-TB drug-related DRESS to resume anti-TB medication, but its clinical usefulness and safety are not validated.

The purpose of this multicenter study was to compare the outcomes and safety of reintroduction methods in patients with anti-TB drug-related DRESS.

Methods

Patient selection

A retrospective cohort of patients with anti-TB drug-related SCARs was established from five different institutions between January 2011 and December 2017 using the Korean SCAR registry, and their medical records were thoroughly reviewed. The inclusion criteria for patients with anti-TB drug-associated SCARs were as follows: patients aged 19 years or older, who were diagnosed with TB, and who developed SCARs due to an anti-TB drug. SCARs were diagnosed according to the RegiSCAR scoring system, which includes the following criteria for DRESS: fever $\geq 38.5^{\circ}\text{C}$, eosinophilia (eosinophils $\geq 0.7 \times 10^9/\text{L}$ or $\geq 10\%$ if white blood cells $< 4.0 \times 10^9/\text{L}$), enlarged lymph nodes, atypical lymphocytes, skin involvement, organ involvement (liver, kidney, lung, heart, bone marrow, or central nervous system), prolonged time to resolution (≥ 15 days), and exclusion of other causes. We considered those with RegiSCAR score ≥ 4 as DRESS.⁶ The following were the criteria for SJS/TEN: hospitalization, widespread exanthema with 1 to $<10\%$ of skin detachment; more than one blister, not only acral involvement, with or without mucous membrane erosions.⁷ The causality assessment of anti-TB drugs as the culprit drugs was performed using World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality assessment system, and cases assessed as ‘certain’ or ‘probable’ were included.

Anti-TB drug reintroduction methods

Three different anti-TB drug reintroduction methods were used for patients with anti-TB drug-related SCARs. The first approach was changing all drugs included in the anti-TB regimen which resulted in SCARs and introducing full therapeutic doses of alternative drugs. The second approach was graded challenge of anti-TB drugs which resulted in SCARs. The discontinued drugs were re-administered one at a time, two to three days apart as shown

Table 1. The third approach was tolerance induction based on desensitization protocol starting from a dose lower than 1/10,000 of the recommended dose and increasing gradually at two-hour intervals as shown in Table 2. The time interval was modified in some cases to 3 hours for drugs that caused breakthrough reactions (BTR) on reintroduction^{8,9} (Table E1).

Patch test

Patch test was done using the Finn chamber (diameter 8 mm) method as described previously with 0.02 mL of drugs that had been taken when SCARs had occurred, diluted 10% in petrolatum.¹⁰ Patches were applied on dry, non-hairy sections of the upper back after cleansing with ethanol.¹¹ The patients returned for reading of the results after 48 h and 72 h, and the results were graded per the International Contact Dermatitis Research Group criteria.¹²

Data collection and outcomes

All data were collected from electronic medical records, including demographic characteristics, latency periods, clinical features of the allergic reactions, responses to reintroduction, and outcomes of anti-TB treatment. The primary outcome was successful resumption of anti-TB drugs, and the secondary outcome was completion of anti-TB treatment. Resumption was regarded as successful if therapeutic doses of anti-TB were maintained without the development of clinically significant hypersensitivity reactions. The resumption was considered unsuccessful if anti-TB drug administration could not be maintained because of flare-up reactions or any other adverse drug reactions. Anti-TB treatment was considered completed when the treatment was ceased by physicians based on evidence of clinical recovery after anti-TB treatment according to TB guidelines.¹³

172 **Ethics statement**

173 This study has been approved by the Institutional Review Board (IRB) of Seoul National
174 University Hospital (IRB No. 1408-021-601). The board waived the need for informed
175 consent.

Results

Patient characteristics

Thirty-one patients with anti-TB drug-associated SCARs were recruited, including 29 cases of DRESS and 2 cases of SJS. Analyzing 29 DRESS patients, their median age was 51 years, ranging from 22 to 81 years, and 45% of them were male (Table 3). None of the patients had a previous history of drug allergies. Patients were treated for active TB infections with first-line drugs only ($n = 22$), second-line drugs only ($n = 2$), or combinations of first and second-line anti-TB drugs ($n = 5$). The median duration of anti-TB medication before the development of SCARs was 28 days (interquartile range 6–194 days). Other clinical characteristics are presented in Table 3.

Causative drugs in anti-TB drug-associated DRESS

Causality of culprit drugs was assessed by WHO-UMC criteria. Although it was difficult to clearly determine the culprit drug(s) as patients were on multiple anti-TB drugs simultaneously at the time of the DRESS development, anti-TB drug(s) with certain or probable causality were identified, at least in part, in 20 patients based on recurrence of hypersensitivity reactions during reintroduction or positive patch test results.

Most of the study patients were not able to hold off on anti-TB treatment to perform patch test for a prolonged period because of their active TB infections. Therefore, patch tests were performed in 9 patients between 6 weeks and 6 months after gross resolution of the cutaneous lesions with at least one month of systemic corticosteroids free period. Six of them were patch test positive (66.7%), and all of them showed multidrug hypersensitivity to at least two different agents; four patients showed positivity to two drugs and the other two patients showed positivity to three drugs (Table E2, Supplementary figure E1). Based on the results of reintroduction or patch tests, median 2 drugs (range = 1-5) per case showed

201 reactivity.

202 **Three different approaches for the re-administration of anti-TB medications in patients**
203 **with DRESS**

204 Anti-TB medications were resumed in 27 patients with DRESS (Figure 1) using three
205 different approaches and 19 patients eventually completed anti-TB treatment (19/29, 65.5%).
206 The anti-TB drugs could not be reintroduced in two patients; one patient died due to
207 aggravation of underlying acute myeloid leukemia and the other patient was lost to follow-up.

208 First, nine patients who experienced SCARs during the treatment with the first-line anti-
209 TB drugs had their anti-TB medication changed to unexposed second-line anti-TB drugs.
210 However, despite complete avoidance of potential culprit drugs, 8 patients (88.9%)
211 experienced drug hypersensitivity reactions to the newly introduced second-line anti-TB
212 drugs. Only one patient, who successfully resumed and maintained anti-TB treatment,
213 underwent patch test before reintroduction and anti-TB drugs were selected based on the
214 result of a patch test.

215 Second, graded challenges with previously administered anti-TB drugs were performed
216 in five patients; two of them (40.0%) completed anti-TB treatment without any problems, but
217 three patients failed to maintain anti-TB treatment due to flare-up reactions. Two of the three
218 patients developed generalized rash on the day of drug challenge, and the other patient
219 developed generalized rash two days later. These three patients resumed anti-TB medication
220 with previously unexposed drugs by graded challenge and succeeded in maintenance of anti-
221 TB medication.

222 Third, a total of 13 patients underwent desensitization with previously administered anti-
223 TB drugs at the onset of DRESS: 11 patients with first-line anti-TB drugs and two patients
224 with second-line anti-TB drugs. All of them reached the therapeutic doses without any serious
225 hypersensitivity reactions and 11 patients (84.6%) could maintain and eventually complete

anti-TB treatment. In addition, four patients underwent desensitization protocol as a second step after the development of hypersensitivity reaction in spite of changing all drugs as the first step (Figure 1). Altogether, a total of 17 patients underwent desensitization to previously administered anti-TB drugs and 15 (88.2%) successfully completed anti-TB treatment. Among 14 patients (82.4%) who experienced BTRs during the desensitization process, 12 patients had mild cutaneous reactions which were adequately managed with antihistamine and two patients developed mild increase of liver enzymes recovered after temporary withhold of the drugs. The success rate was varied by drugs (Table E3).

Clinical course of patients who failed to resume anti-TB medication

Eight out of 9 patients with DRESS who were re-initiated with previously unexposed second-line anti-TB drugs failed to maintain anti-TB treatment. Three patients gave up the anti-TB treatment since two of them developed flare up of DRESS and the other had severe generalized rash and itching despite complete avoidance of the suspected culprit drugs. Five patients tried resumption of anti-TB treatment again; one of them underwent graded challenge but the anti-TB treatment was stopped due to recurrence of DRESS. The other four patients were started on desensitization and two of them (50%) finally succeeded in maintaining anti-TB medication (Figure 1).

Three of five patients who underwent a graded challenge experienced maculopapular eruptions; two of them developed the rash on the day of isoniazid reintroduction and the other patient developed the rash three days after taking cycloserin and prothionamide.

Two of 13 patients who underwent desensitization as a first step eventually discontinued anti-TB treatment due to the late onset adverse drug reactions after initially successful desensitization; one discontinued anti-TB drugs due to persistent itching and the other patient stopped the drugs due to newly developed drug-induced liver injury (DILI) without any skin

manifestations. Among four patients who underwent desensitization as a second step after the failure to resume anti-TB medication by changing all drugs, two eventually failed to maintain the anti-TB medications because of DILI.

Two Cases of SJS

In two cases of SJS, patch testing was performed in one patient before reintroduction of anti-TB drugs and showed positivity to two different agents (PZA, EMB). Two patients with SJS underwent desensitization with previously administered anti-TB drugs except for the culprit drugs and eventually completed anti-TB treatment by adding some previously unexposed second-line anti-TB drugs.

Discussion

Our study shows that desensitization can be considered a safe and generally well tolerated option in patients who developed anti-TB drug-related DRESS especially when there are no effective alternative drugs. So far, there has been no evidence-based recommendation to perform desensitization in patients who experience DRESS. This study shows the result that favors the implementation of desensitization in patients with anti-TB drug-related DRESS to resume anti-TB medication; desensitization seems to be an effective and safer option when compared to graded challenges or resuming with unexposed drugs. Table 4 summarizes the general information for each treatment.

If anti-TB medication-related hypersensitivity reactions are suspected, it is recommended to discontinue all the drugs and reintroduce by graded challenges with previously administered drugs. However, in cases of DRESS, graded challenges have a high risk of eliciting another severe hypersensitivity reaction. In fact, 60% of patients who attempted a graded challenge failed to achieve maintenance treatment in this study. If causative agents could be identified, it would be much safer to perform graded challenges without the culprit agents. However, identifying the culprit drugs is difficult because there is no test with satisfactory sensitivity and specificity in real practice. A Cochrane review of T cell mediated sulfonamide antibiotic hypersensitivity showed that the fewer discontinuation rate with desensitization when compared to the full dose rechallenge.¹⁴ This finding is potentially relevant in the setting of resuming anti-TB treatment in DRESS as discontinuation rate should be kept to a minimum while the treatment needs to be restarted quickly.

Patch tests can be applied to patients with delayed cutaneous hypersensitivity reactions but only a few detailed studies have determined their sensitivity and specificity. In DRESS, patch test sensitivity is reported to be between 32% to 64% depending on the drug.¹⁵ While the specificity is generally considered high, false-positivity can occur due to irritation.

Therefore, multiple positivity in patch test could be due to false-positivity. On the other hand, DRESS often shows multiple drug hypersensitivity (MDH), therefore multiple positivity in this setting could be true positive.¹⁶⁻¹⁹ There is *in vivo* test for immunological mechanism of MDH analyzing peripheral blood, drug-reactive T cells are found in a pre-activated cell fraction which may lead a lower threshold for activation by drugs.^{20, 21} In several *in vitro* studies comparing MDH and mono allergy patients, sustained T-cell activation was found from MDH.¹⁷ It could be an explanation for patch tests were positive to > 1 drug.

In addition, patch tests cannot be performed on inflamed skin during the active phase of DRESS. Since resuming anti-TB medication should not be delayed due to the risk of TB reactivation and development of drug resistance, it is not ideal to postpone anti-TB medication long enough for skin to recover for patch test. As a result, in this study, only two cases could undergo patch testing before the first reintroduction of anti-TB medication.

In this setting, lymphocyte transformation tests can be performed, however, it is not readily available and is operator dependent.^{17, 22} In addition, the sensitivity is not well established and varies according to the drug, and there is no standardized protocol for anti-TB drugs. An intradermal test can also be considered to evaluate culprit agents but it was not appropriate to perform in the acute phase and is not readily available for drugs that are some drugs.

Changing all the drugs to previously unexposed drugs is one of the reintroduction options. However, in the cases of anti-TB treatment, conversion to the second line drugs is unfavorable in terms of drug efficacy and duration of treatment, therefore it is often difficult to complete the treatment of TB. Furthermore, in patients with anti-TB drug-related DRESS, multiple drug hypersensitivity reaction can occur where drugs without immunologic memory or even newly administered drugs can provoke hypersensitivity reactions.^{21, 23} Clinically, it is difficult to distinguish whether the drugs that induce hypersensitivity reactions are true

allergic reaction with accompanying drug-specific T cell response or whether the symptoms involve non-specific activation of the immune system without memory response. In either cases, reintroduction of drugs can result in recurrence of hypersensitivity reactions resembling DRESS. In this study, 89% of patients resuming anti-TB drugs that had not been administered previously experienced hypersensitivity reactions. Therefore, anti-TB drugs should be re-administered with caution.

Reintroduction of potential culprit agents is generally contraindicated in patients with DRESS because the potential risk of DRESS recurrence.²⁴ However, given dose-dependent T cell response in DRESS,²⁵ desensitization may result in less severe reaction or tolerance induction. Therefore, desensitization protocol can be considered as an alternative option in resuming anti-TB drugs including potential culprit drugs and this study shows promising results.

Drug desensitization is a method to induce an 'immune tolerance' state of the immune system to the therapeutic dose of a culprit drug by gradually increasing the amount of drug from a very small amount below 1/10,000 of the dose inducing hypersensitivity reactions. In the past, desensitization was mainly implemented for immunoglobulin E-mediated immediate hypersensitivity reactions, but it has also been used for T-cell-mediated delayed hypersensitivity reactions recently.⁴

In recent years, the results of desensitization therapy performed in patients with delayed hypersensitivity reactions have been reported; success rates were dependent on the type of drug, clinical features, and desensitization protocols.⁴ Since Holland et al. had reported rapid desensitization to isoniazid and rifampin in 1990,²⁶ successful cases of desensitization to anti-TB drugs through oral and intravenous antibiotics have been reported for various anti-TB drugs.^{8, 9, 27-29} However, there is no standardized protocol or guideline for the desensitization of delayed type hypersensitivity induced by anti-TB drugs currently, and its mechanism of

tolerance induction is not clearly known, especially for cases of DRESS.

The exact mechanism behind desensitization in T cell hypersensitivity is unknown. It was shown that Treg population was increased after desensitization in patients with fixed drug eruption.³⁰ Therefore, it is plausible that antigen-reactive T-cells might be controlled by these enhanced Tregs. In the study of T cells reactivity in allopurinol hypersensitivity, the T cell response was remarkably decreased from a dose as low as 1/100, and the dose-response curve showed remarkable steepness.²⁵ Therefore, it can be speculated that desensitization from a very small dose can bypass the antigen-reactive T-cell reaction by avoiding the threshold to activate T cells. Although the rapid desensitization protocol is usually implemented in an immediate response, there are several cases in which desensitization was performed by rapid protocol in case of non-immediate hypersensitivity due to antibiotics and chemotherapy agents with high success rate, but the mechanism is not yet known.³¹⁻³³

In general, almost 60–80% of patients who were hypersensitive to standard anti-TB treatment can continue the standard first-line treatment without discontinuing anti-TB drugs through desensitization protocol.³⁴⁻³⁶ The results of the current study also support the application of desensitization protocol even in cases of anti-TB drug-related DRESS.

In terms of safety, although BTRs developed during the build-up period in 82.4% (14/17) of patients who underwent desensitization, all of them were mild ones resolved with temporary discontinuation of the drug and none of them progressed to recurrence of DRESS. Therefore, it seems to be safer than reintroducing by other methods such as graded challenges or changing to previously unexposed drugs. Based on the findings of this study as well as the previous reports on resuming anti-TB drugs in patients with DRESS, reintroduction based on desensitization protocol may be considered a safer option to resume anti-TB treatment.

Despite the successful build up to therapeutic dose, maintenance treatment may fail because of the delayed onset adverse reactions. In this study, there was three patient with

DRESS who presented with DILI; while two patients failed to maintain the anti-TB medications due to elevation of liver enzymes with skin symptom during desensitization, the other one had unexpected liver enzyme elevations one month after resuming anti-TB medication based on desensitization protocol. However, it is unclear whether or not DILI was related to relapse of DRESS. Considering the absence of cutaneous reactions or other characteristic features of DRESS, the isolated DILI case developed one month later might have been a separate event unrelated to the anti-TB drugs induced SCAR. However, given DILI is also T cell mediated, immunologic activation could not be ruled out. There was one patient who presented with delayed onset chronic itching, but the clinical manifestation was not consistent with the relapse of DRESS. Therefore, it is necessary to further evaluate whether these delayed onset drug reactions may be related to the initial DRESS.

The limitations of this study are its retrospective design and the lack of patch testing results in some patients. DRESS usually take several weeks for the resolution of skin lesions and tapering of immune suppressants. In previous studies, patch tests were performed 6 weeks to 6 months after complete healing of cutaneous adverse drug reactions¹¹ and at least 1 month after discontinuing systemic corticosteroids¹⁰ but timely patch testing for the reintroduction of anti-TB drugs is difficult in reality. Since this is an uncontrolled retrospective cohort study, selection bias could have occurred in choosing the re-administration method. While there is no proven severity index of DRESS, based on the RegiSCAR score of DRESS at the time of the diagnosis, the patients who had undergone desensitization were not less severe (median 5, range 4 to 8) compared to those who underwent graded challenge (median 5, range 4 to 6) and those who changed all drugs (median 6, range 4 to 7). The study was also limited by a small heterogeneous cohort and non-standardized desensitization protocols implemented for the reintroduction of anti-TB drugs. Although a rapid desensitization protocol in which the dose is doubled every 15

minutes is widely used for immediate hypersensitivity reactions, there are only a few studies that have validated protocols for delayed hypersensitivity, especially in DRESS. Therefore, more researches looking at different protocols are required to establish standard desensitization protocols for cases of anti-TB drug-related DRESS. In addition, since the number of patients who underwent graded challenge or those with SJS were small, a future larger study including not only DRESS but also SJS with different reintroduction methods is needed.

Despite these limitations, desensitization protocol to resume anti-TB medication in DRESS patients might contribute to the control of TB reducing treatment interruption by enabling effective and safe anti-TB treatment if it can be appropriately performed and closely monitored.

In conclusion, the implementation of a desensitization protocol for anti-TB drug-associated DRESS is a safe and effective way to resume anti-TB drug administration and long-term monitoring is needed to detect delayed reactions.

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495 **Figure legend**

496 Figure 1. Reintroduction of anti-TB treatment in patients with SCARs

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497 Table 1. An example of graded challenge protocol for 1st line antituberculous drugs

	Day1	Day2	Day3	Day4	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12
Rifampin (mg)	150	300	450	600	600	600	600	600	600	600	600	600	600
Isoniazid (mg)					100	200	300	300	300	300	300	300	300
Pyrazinamide (mg)								500	1000	1500	1500	1500	1500
Ethambutol (mg)											400	800	1200

498 Patients body weight $\geq$ 50 kg

499 Table 2. An example of isoniazid desensitization protocol (target dose: 300 mg)

	Step	Concentration (mg/mL)	Amount (mL)	Time (hr)	Administered dose (mg)	Cumulative dose (mg)
D1	1	0.2	0.1		0.02	0.02
	2	0.2	0.2	2hr	0.04	0.06
	3	0.2	0.5	2hr	0.1	0.16
	4	0.2	1	2hr	0.2	0.36
	5	0.2	2	2hr	0.4	0.76
	6	0.2	4	2hr	0.8	1.56
	7	0.2	8	2hr	1.6	3.16
	8	0.2	16	2hr	3.2	6.36
D2	9	2.0	3		6	12.36
	10	2.0	6	2hr	12	24.36
	11	2.0	12	2hr	24	48.36
	12	100 mg Tab	0.5Tab	2hr	50	98.36
	13	100 mg Tab	1Tab	2hr	100	198.36
	14	100 mg Tab	2Tab	2hr	200	398.36
D3	15	100 mg Tab	3Tab		300	300

500 T: tablet

501 Table 3. Clinical characteristics of antituberculous drug associated severe cutaneous adverse reaction cases.

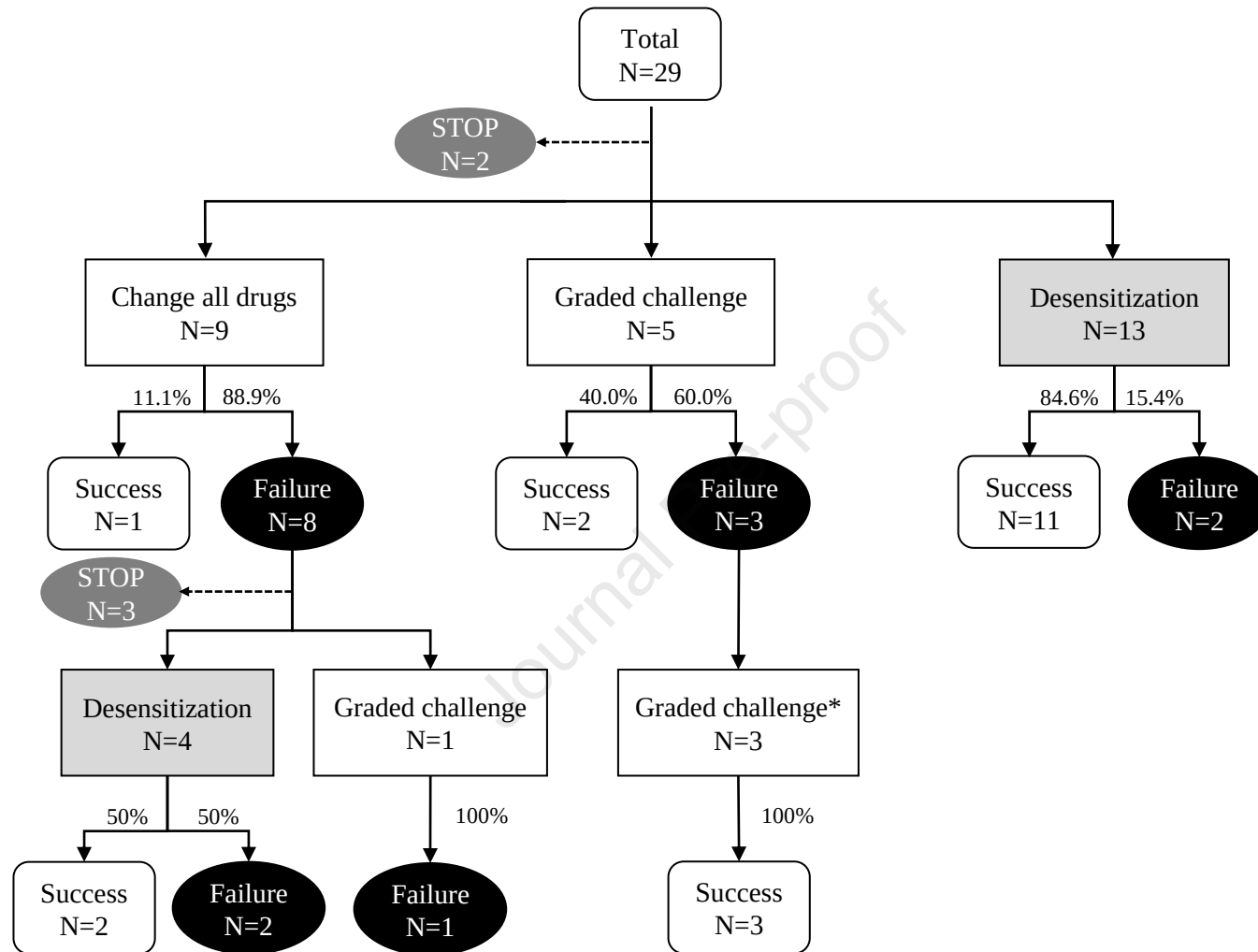
Age (years), median (range)	51 (22-81)
Male sex, n (%)	13 (45)
Type of tuberculosis	
Pulmonary, n (%)	18 (62)
Extra-pulmonary, n (%)	10 (35)
Disseminated, n (%)	1 (3)
Result of mycobacterial culture; positive, n (%)	18 (62)
Latency period, day, median (IQR)	28 (6-194*)
Hospitalization due to SCAR, n (%)	25 (86)
Skin rash, extent (%), median (IQR)	100 (22.5-100)
Fever >38°C, n (%)	21 (72)
Enlarged lymph nodes, n (%)	1 (3)
Laboratory findings at diagnosis	
WBC (/mm ³), median (IQR)	8580 (310-59,140)
Lymphocyte (/mm ³), median (IQR)	1,564 (120-23,064)
Atypical lymphocytes, n (%)	14 (48)
Eosinophil (/mm ³), median (IQR)	1,628 (30-7,991)
Platelet (x10 ³ /mm ³), median (IQR)	114 (1-336)
ALT (U/uL), median (IQR)	137 (25-1808)
Creatinine (mg/dl), median (IQR)	0.86 (0.5-5.1)
Duration of SCARs (day), median (IQR)	62 (4-488)

502 IQR: Interquartile Range; *One patient developed DRESS 194 days after starting antituberculous treatment; rifampicin was added to the existing regimen 42 days before the
503 onset. Although rifampicin was the suspected culprit, in the process of re-administration, the patient developed a systemic rash and itch due to ethambutol and cycloserin
504 which the patient had taken from the beginning. Therefore, the latency period was set for 194 days as the previously used drugs could not be ruled out as the culprit.

Table 4. Overview of the patients' anti-tuberculous treatment

Patient	Diagnosis	Initial anti-TB drugs	1st reintroduction	2nd reintroduction	Final regimen	Anti-TB treatment outcome	Confirmed reactants
M/46	DRESS	INH/RIF/EMB/PZA	Change all drugs	-	Cs/Lfx/Km	Success	NA
M/81	DRESS	INH/RIF/EMB/PZA	Change all drugs	-	PZA/Lfx	Failure d/t DRESS	NA
M/78	DRESS	INH/RIF/EMB/PZA	Change all drugs	-	EMB/Mfx/Cs/Am	Failure d/t DRESS	NA
F/36	DRESS	INH/RIF/EMB/PZA	Change all drugs	-	EMB/Cs/Pto/Mfx	Failure d/t rash, itching	NA
M/25	DRESS	INH/RIF/EMB/PZA	Change all drugs	Graded challenge	PZA/Mfx/Cs	Failure d/t DRESS	INH, EMB
F/46	DRESS	INH/RIF/EMB/PZA	Change all drugs	Desensitization	EMB/Mfx/S	Failure d/t DILI	INH, RIF, Cs
F/42	DRESS	INH/RIF/EMB/PZA	Change all drugs	Desensitization	INH/RIF	Failure d/t DILI	RIF, EMB, PZA, Cs
F/55	DRESS	INH/RIF/EMB/PZA	Change all drugs	Desensitization	INH/RIF/PZA	Success	INH, RIF, EMB, Mfx, Cs
F/34	DRESS	INH/RIF/EMB/PZA	Change all drugs	Desensitization	RIF/Lfx/Cs	Success	INH, PZA, Pto
M/56	DRESS	INH/RIF/EMB/PZA	Graded challenge	-	INH/EMB/Mfx	Success	NA
M/22	DRESS	INH/RIF/EMB/PZA	Graded challenge	-	INH/RIF/PZA	Success	NA
F/38	DRESS	INH/RIF/EMB/PZA	Graded challenge	Graded challenge (same drugs)	RIF/EMB /PZA	Success	INH
F/38	DRESS	INH/RIF/EMB/PZA	Graded challenge	Graded challenge (drugs changed)	RIF/PZA/Mfx/S	Success	INH, EMB
F/70	DRESS	RIF/EMB/PZA/Mfx/Cs/S	Graded challenge	Graded challenge (drugs changed)	PZA/PAS/Amx-Clv/Clari	Success	EMB, Pto, Cs
M/80	DRESS	INH/RIF/EMB/PZA	Desensitization	-	INH/Lfx/Cs/Pto	Success	RIF, PZA
M/60	DRESS	INH/RIF/EMB/PZA	Desensitization	-	INH/PZA/Lfx	Success	RIF, EMB
F/37	DRESS	INH/RIF/EMB/PZA	Desensitization	-	INH/RIF	Success	INH, EMB
F/72	DRESS	INH/RIF/EMB/PZA	Desensitization	-	INH/PZA/Lfx	Success	RIF
F/38	DRESS	INH/RIF/EMB/Lfx	Desensitization	-	INH/EMB/PZA	Success	Lfx
F/47	DRESS	INH/RIF/PZA/Mfx	Desensitization	-	INH/RIF/PZA/Lfx	Success	INH, Mfx
M/51	DRESS	PZA/Lfx/PAS/Pto/Cs	Desensitization	-	Lfx/Cs/Amx-Clv	Success	Pto, PAS
F/22	DRESS	Mfx/PAS/Pto/Cs/KM	Desensitization	-	Cs/Lfx/PZA	Success	Pto
M/65	DRESS	INH/RIF/EMB/PZA	Desensitization	-	INH/EMB/Mfx	Success	RIF, PZA
F/68	DRESS	INH/RIF/EMB/PZA	Desensitization	-	INH/PZA/Lfx	Success	INH, RIF, EMB, PZA
F/78	DRESS	INH/RIF/EMB/PZA	Desensitization	-	Lfx/Cs/PAS/Amx-Clv	Success	INH, RIF, EMB, PZA
M/68	DRESS	INH/RIF/EMB/PZA	Desensitization	-	INH/PZA/Lfx/Am	Failure d/t DILI	RIF, EMB, PAS
F/81	DRESS	INH/RIF/Mfx	Desensitization	-	INH/PZA/Mx	Failure d/t itching	NA

RIF rifampin; INH isoniazid; PZA pyrazinamide; EMB ethambutol; Lfx levofloxacin; Mfx moxifloxacin; Pto prothionamide; Cs cycloserin; KM kanamycin; S streptomycin; PAS p-aminosalicylic acid; Am Amikacin; Amx-Clv Amoxicillin/Clavulanic acid; DRESS drug reaction with eosinophilia and systemic symptoms; SJS Stevens-Johnson syndrome; DILI Drug Induced Liver Injury



*Graded challenge with other drugs except those with severe BTR in the first trial or previously unexposed drugs

Figure E1. The patch test result of a patient as an example

Read at 48 hours (A), and 72 hours (B). Test drugs are isoniazid (INH), rifampin (R), pyridoxine (P), sulfamethoxazole-trimethoprim (sep), p-aminosalicylic acid (PAS), kanamycin (K), linezolid (zyv), cycloserine (CS), levofloxacin (LV), pyrazinamide (PZA), ethambutol (E), vaseline (V) in clockwise direction from the right top. INH and CS were ++ at 48 hours and 72 hours.

