

# Severe cutaneous adverse drug reactions due to antituberculosis drugs and their management

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## ABSTRACT

**OBJECTIVE:** Tuberculosis and drug reactions due to antituberculosis drugs are important public health problems. Severe cutaneous adverse drug reactions (SCARs) due to antituberculosis drugs are factor that makes tuberculosis treatment difficultchallenging. In this real-life study, we present our experience with SCARs due to antituberculosis drugs and their management.

**METHODS:** Patients hospitalized in the tuberculosis ward of tertiary care reference hospital between January 1, 2015, and September 1, 2023, were retrospectively reviewed. Patients who consulted the immunology and allergy clinic were included in the study.

**RESULTS:** A total of 4,039 patients were hospitalized with tuberculosis during the study period. A total of 316 (7.8%) patients were consulted, and out of these, eight (2.5%) patients were evaluated as SCARs. Of the eight patients, seven (87.5%) were diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS), and one was diagnosed with Stevens-Johnson syndrome (SJS) (12.5%). The peripheral blood eosinophil count of patients with DRESS ranged between 740 and 8,690 cells/ $\mu$ L. One patient tested positive for human immunodeficiency virus and developed SJS. Methylprednisolone intravenous 1 mg/kg and Fexofenadine 180 mg/day per oral were used in the treatment of SCARs in all cases. Ad-on treatment for three cases used mepolizumab (anti-IL5 monoclonal antibody) for DRESS. All patients were switched to an alternative treatment protocol and tolerated the new regimen well.

**CONCLUSION:** In cases with developed SCARs, a new treatment protocol consisting of different medications can be applied after the symptoms improve. DRESS was the most common SCAR of antituberculosis drugs. Monitoring the eosinophil count can help in early diagnosis. Systemic steroids and antihistamines may be effective in the treatment. Mepolizumab can be used with off-label approval in the treatment of DRESS cases to accelerate the treatment process.

*Keywords: Antituberculosis drug hypersensitivity; drug reaction; drug reaction with eosinophilia and systemic symptoms (DRESS); mepolizumab; severe cutaneous drug reactions; stevens-johnson syndrome (SJS).*

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Tuberculosis is a contagious and potentially lethal disease that causes significant health issues. Based on current treatment recommendations, 85% of patients can be cured when treated for four to six months [1]. Adverse

drug reactions (ADRs) that occur during treatment are a significant public health concern for both the patient and the community. ADRs to antituberculosis drugs include hepatitis, cutaneous ADRs, nausea/vomiting, influen-

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za-like illness, and arthralgia [2]. In a previous study, the rate of immediate-type hypersensitivity reactions to first-line antituberculosis drugs was found to be 3.4% [3]. The prevalence of drug reactions in hospitalized tuberculosis patients was reported to be 7.8%. [4].

Severe cutaneous adverse reactions (SCARs) may involve only the skin or may also be life-threatening reactions. The definition of SCARs includes various entities such as generalized bullous fixed drug eruptions, acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN) [5]. These non-immunoglobulin E-mediated hypersensitivity reaction patterns can range from simple cutaneous drug eruptions caused by immunological mechanisms to severe clinical presentations involving organs such as the liver or hematological abnormalities [6]. In the database of the Korean Registry of SCAR, it was reported that antituberculosis drugs were involved in the etiology of 53 (6.7%) out of 783 SCAR patients [7]. The frequency of DRESS caused by antimycobacterial drugs ranked 8<sup>th</sup> (6.2%) among drug classes [8].

There are various diagnostic and therapeutic approaches for different conditions in SCARs. Managing SCARs associated with antituberculosis drugs presents challenges such as time constraints for treatment, limitations on corticosteroid use, and the need to sustain tuberculosis treatment. This study aimed to present our clinical experience with SCARs related to antituberculosis drugs and their management.

## MATERIALS AND METHODS

Patients hospitalized in the tuberculosis ward of a tertiary care reference hospital between January 1, 2015, and September 1, 2023, were retrospectively reviewed. Patients who consulted the immunology and allergy clinic were included in the study. Those who were consulted and diagnosed with SCARs were documented. Demographic data, diagnosis, anti-tuberculosis drugs used, diagnosis of SCARs, Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scores of patients with DRESS, medications used in the treatment of SCARs, and anti-tuberculosis drug treatment after SCARs were recorded. A skin patch test was performed in the early period immediately after the clinical picture improved. This tests were prepared with 10% and 30% petrolatum Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital ethics committee approval

### Highlight key points

- Severe cutaneous adverse reactions may cause serious problems during treatment with antituberculosis drugs.
- An early indicator for DRESS may be an increase in peripheral blood eosinophils.
- The use of anti-IL-5 treatments (mepolizumab) may help accelerate the recovery process in DRESS treatment.

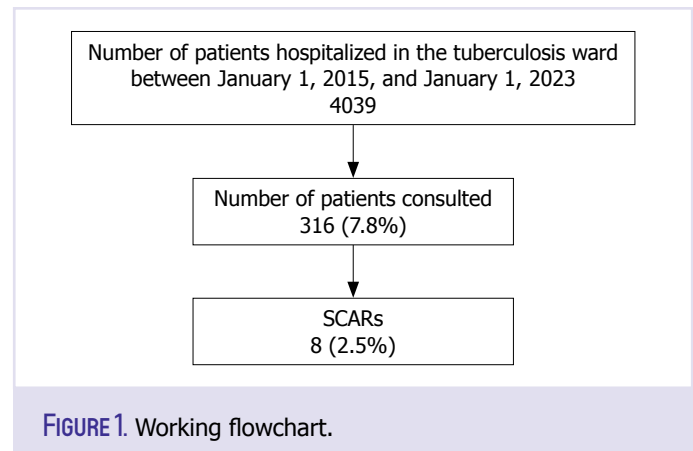


FIGURE 1. Working flowchart.

was obtained for the study (07-09-2023/116.2017.R-311). This study was conducted in accordance with the Declaration of Helsinki.

## RESULTS

During the study period, 4,039 patients were hospitalized in the tuberculosis ward for inpatient examination and treatment. A total of 316 (7.8%) patients were consulted, and out of these, eight (2.5%) patients were evaluated as SCARs. The working flowchart is shown in Figure 1.

Of the eight patients diagnosed with SCARs, four were male (50%) and four were female (50%). The patients were between 30 and 70 years of age. Of the eight patients, seven (87.5%) were diagnosed with DRESS, and one was diagnosed with SJS (12.5%). The RegiSCAR (Registry of Severe Cutaneous Adverse Reactions) score of cases with DRESS was four (probable DRESS) in six cases and three (possible DRESS) in one case. Elevated liver enzymes were observed in four out of seven DRESS cases. Demographic and clinical characteristics of patients are presented in Table 1. In six cases, SCARs developed during the treatment of drug-resistant tuberculosis with HRZE (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol). In two cases, SCARs developed during Multidrug Resistant Tuberculosis (MDR-TB) treatment.

TABLE 1. Characteristics and demographic information of the cases

PN	Age	G	Tuberculosis diagnosis	Culprit drugs	SCARs diagnosis	Reaction time (day)	RegiSCAR score for DRESS	Eosinophil count cells/ $\mu$ l	Treatment of reaction	Diagnostic patch test	New treatment protocol
1	70	F	Pleural	HRZE	DRESS	12	4	1670	Methylprednisolone Fexofenadine	Negative	Amikacin PAS Protonamid Cycloserine
2	52	M	Pulmonary	HRZE	DRESS	18	4	1620	Methylprednisolone Fexofenadine Mepolizumab	Negative	Amikacin PAS Protonamid Cycloserine Moxifloxacin
3	30	F	Pulmonary MDR+	Ethambutol Amikacin PAS Moxifloxacin Protonamid Cycloserine	DRESS	29	4	3140	Methylprednisolone Fexofenadine	Protonamid 30% Sikloserin 10%+	Ethambutol Levofloxacin Bedaqualine Clofazamine
4	67	M	Pulmonary	HRZE	DRESS	17	4	2510	Methylprednisolone Fexofenadine Mepolizumab	Negative	Amikacin PAS Protonamid Cycloserine Levofloxacin
5	57	M	Pulmonary	HRZE	DRESS	58	4	1240	Methylprednisolone Fexofenadine	Negative	Amikacin PAS Protonamid Cycloserine Moxifloxacin
6	62	M	Meningitis	HRZE	SJS	60	-	470	Methylprednisolone Fexofenadine	Negative	Amikacin Protonamid Cycloserine Moxifloxacin Linezolid

TABLE 1 (CONT). Characteristics and demographic information of the cases

PN	Age	G	Tuberculosis diagnosis	Culprit drugs	SCARs diagnosis	Reaction time (day)	RegiSCAR score for DRESS	Eosinophil count cells/ $\mu$ L	Treatment of reaction	Diagnostic patch test	New treatment protocol
7	33	F	Pulmonary MDR+	Moxifloxacin Streptomycin Ethambutol Pyrazinamide Amikacin PAS	DRESS	34	3	740	Methylprednisolone Fexofenadine Mepolizumab	Protonamid 30%+ Sikloserin 10%+ Pyrazinamide 30%	Levofloxacin Bedaquiline Clofazamine Linezolid Delamanide
8	65	F	Pulmonary	HRZE	DRESS	25	4	8960	Methylprednisolone Fexofenadine	Negative	PAS Protonamid Cycloserine Levofloxacin

<sup>a</sup>MDR: Multi drug resistant; <sup>b</sup>HRZE: Isoniazid, rifampicin, pyrazinamid, ethambutol; <sup>c</sup>PAS: Para-aminosalicylic acid; <sup>d</sup>DRESS: Drug reaction with eosinophilia and systemic symptoms; <sup>e</sup>SJS: Stevens-Johnson syndrome; G: Gender; F: Female; M: Male; PN: Patient no

The peripheral blood eosinophil count of patients with DRESS ranged between 740 and 8,690 cells/ $\mu$ L. Skin patch tests with HRZE were negative. In cases of MDR-TB, skin patch tests were positive for cycloserine and protonamide in one case, and for cycloserine, protonamide, and pyrazinamide in the other case. Methylprednisolone intravenous (IV) 1 mg/kg and Fexofenadine 180 mg/day per oral (PO) were used in the treatment of SCARs in all cases. Additionally, in three patients, the anti-IL-5 drug mepolizumab was administered at 100 mg for the treatment of DRESS. All patients were switched to an alternative treatment protocol and tolerated the new regimen well. In a patient diagnosed with MDR-TB, ethambutol was included in both the old and new treatment protocols.

## DISCUSSION

Overall, the primary approach to managing all SCARs is to identify and eliminate the culprit drug [6]. DRESS typically occurs two to eight weeks after starting the medication [9]. In our cases, the reaction time ranged between 12 and 60 days. Eosinophilia can be observed only in 60–70% of cases with DRESS [10]. All of our DRESS patients had eosinophilia. Except for one case, all patients had hypereosinophilia (>1500 cells/ $\mu$ L). Basal eosinophil counts of the patients before the initiation of tuberculosis treatment were normal (<500 cells/ $\mu$ L).

The culprit drug is generally not identified in 10–20% of DRESS cases [11]. Identifying the culprit drug is challenging due to the simultaneous use of multiple drugs in tuberculosis treatment. Skin patch tests to identify the culprit drug in DRESS should be conducted six months after the reaction symptoms recover, with positivity rates ranging from 32% to 64% depending on the specific drug [12]. In a review, patch tests were recommended to be performed four weeks after steroid treatment and four to six weeks after the reaction in patients with DRESS [13]. However, the patients were diagnosed with tuberculosis, and immediate treatment initiation was necessary. Therefore, in our cases, a skin patch test was performed in the early period immediately after the clinical picture improved. Since these tests were not standardized, they were prepared with 10% and 30% petrolatum. Except for two cases of MDR, patch tests were negative. The negative results of these tests can be attributed to their early application.

DRESS cases involving all first-line antituberculosis drugs (HRZE and streptomycin) have been reported in the literature. Rifampicin has been reported as the

most common antituberculosis drug causing DRESS [13, 14]. In one case, both ethambutol and isoniazid-induced DRESS were reported [15]. Skin patch tests with cycloserine and protionamide were positive in two MDR-TB cases. Furthermore, one MDR-TB patient had a positive skin patch test with pyrazinamide, in addition to cycloserine and protionamide. In the literature, there is no standardization of irritant concentrations, and there is a lack of data on the specificity and sensitivity of skin patch tests with these drugs. Nevertheless, these drugs that showed positive patch tests were not included in the new treatment protocol and were not used.

Methylprednisolone (IV) and fexofenadine (PO) (7–14 days) were used in the treatment of all patients with SCARs. In three pulmonary tuberculosis patients, one of whom was MDR-TB, a rapid increase in peripheral blood eosinophil count was observed when the steroid dose was reduced. There was also concern that steroids may cause tuberculosis progression due to their immunosuppressant effect. In these three patients, mepolizumab 100 mg every four weeks subcutaneously (with off-label approval) was administered to expedite the DRESS treatment process and promptly initiate new antituberculosis treatment. These patients are the first cases in which mepolizumab was utilized in the treatment of DRESS caused by antituberculosis drugs. There are case reports in the literature on the use of mepolizumab in the treatment of DRESS related to various drugs [16, 17]. Two patients received three doses at 28-day intervals, while one patient received a single dose of mepolizumab. After the first administration of Mepolizumab, eosinophil counts decreased rapidly, and steroid treatment was not required.

Upon recovery of DRESS, a new antituberculosis treatment protocol was planned for the patients. This basic strategy was implemented to prevent SCAR recurrence and to initiate tuberculosis treatment promptly. The treatment regimen administered to patients is detailed in Table 1.

One patient developed SJS after receiving HRZE. This patient tested positive for Human Immunodeficiency Virus (HIV). However, the patient was not on any antiviral treatment. A skin biopsy was also performed on this patient, confirming the diagnosis of SJS. When the patient's symptoms improved, a treatment protocol involving new antituberculosis drugs was initiated, and the patient tolerated it well. On the other hand, desensitiza-

tion to the same antituberculosis drugs was reported in an HIV-positive patient who developed SJS due to the anti-tuberculosis drug [18].

In the database of the Korean Registry of SCAR, it was observed that the frequency of DRESS in SCARs due to antituberculosis drugs was higher than in SCARs due to non-antituberculosis drugs (77.4% vs. 45.8%,  $p < 0.001$ ) [7]. In our cases, DRESS was observed in seven patients (87.5%) and SJS in one patient (12.5%). Consistent with the literature, DRESS was the most common presentation of SCARs related to antituberculosis drugs.

The overall mortality rate for DRESS is reported to be between 3.8% and 10%, and between 19.4% and 29% in SJS [13, 19]. No mortality was observed in our cases.

Information on genetic predisposition and viral reactivation in the pathogenesis of DRESS is available in the literature. Human Herpesvirus-6 (HHV-6) is most commonly associated with DRESS, although other human herpesviruses have also been reported, including HHV-7, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Herpes Simplex virus [20, 21]. No tests for viral reactivation were performed in our DRESS cases, which is a limitation of our study. There are two *in vitro* tests, the lymphocyte transformation test (LTT) and the enzyme-linked immunospot (ELISpot) assay, which can be used to help identify the culprit drug [22]. High sensitivity and specificity have been reported for anti-TB drugs with LTT (sensitivity: 87.5%, specificity: 100%;  $p = 0.004$ ) [22]. Due to the difficulty in accessing the test, the LTT for moxifloxacin and streptomycin could only be performed in MDR case number 7, resulting in a negative outcome. In this case, another quinolone group antibiotic (levofloxacin) was safely used in the new treatment protocol. The inability to perform LTT and ELISpot assays in all of our patients is another limitation of our study.

There were some limitations in the present study. First, it was a retrospective, single-center study. Nonetheless, it provides crucial clinical information due to the sample size and specific patient groups. Besides, study is performed in the tertiary care hospital which is the largest reference center. Data were collected electronically from the hospital online database to prevent incorrect and missed data entry. Second the results were not generalized to whole population. These results may be helpful for physicians managing patients who had SCARs due to antituberculosis drugs.

## Conclusion

The most common SCAR caused by anti-tuberculosis drugs is DRESS. The diagnostic approach is difficult due to the use of many drugs in treatment. Monitoring eosinophil count may serve as an early warning laboratory result in symptomatic patients. Especially in the treatment of DRESS, mepolizumab can be used for early recovery in addition to systemic steroids and antihistamines with off-label approval. When symptoms improve, implementing a new treatment protocol that excludes the use of old medications may enable treatment to continue without interruption.

**Ethics Committee Approval:** The Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee granted approval for this study (date: 07.09.2023, number: 116.2017.R-311).

**Informed Consent:** Written informed consents were obtained from patients who participated in this study.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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## REFERENCES

- World Health Organization. Global tuberculosis report 2022. Geneva: World Health Organization; 2022. Accessed: <https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2022> Available at 21 November, 2025.
- Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. *Expert Opin Drug Saf* 2006;5:231-49. [\[Crossref\]](#)
- Buhari GK, Keren M, Dursun AB, Güler M, Dulkar G, Kalaç N, et al. Immediate-type hypersensitivity reactions due to antituberculosis drugs: a successful readministration protocol. *Ann Allergy Asthma Immunol* 2015;115:39-44. [\[Crossref\]](#)
- 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. [\[Crossref\]](#)
- Cho YT, Chu CY. Treatments for Severe Cutaneous Adverse Reactions. *J Immunol Res* 2017;2017:1503709. [\[Crossref\]](#)
- Owen CE, Jones JM. Recognition and Management of Severe Cutaneous Adverse Drug Reactions (Including Drug Reaction with Eosinophilia and Systemic Symptoms, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis). *Med Clin North Am* 2021;105:577-97. [\[Crossref\]](#)
- Jin HJ, Kang DY, Nam YH, Ye YM, Koh YI, Hur GY, et al. Severe Cutaneous Adverse Reactions to Anti-tuberculosis Drugs in Korean Patients. *Allergy Asthma Immunol Res* 2021;13:245-55. [\[Crossref\]](#)
- Li D, Gou J, Zhu J, Zhang T, Liu F, Zhang D, et al. Severe cutaneous adverse reactions to drugs: A real-world pharmacovigilance study using the FDA Adverse Event Reporting System database. *Front Pharmacol* 2023;14:1117391. [\[Crossref\]](#)
- Tashiro Y, Azukizawa H, Asada H, Niihara H, Morita E, Yamauchi T, et al. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms due to lamotrigine differs from that due to other drugs. *J Dermatol* 2019;46:226-33. [\[Crossref\]](#)
- Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol* 2007;156:1083-4. [\[Crossref\]](#)
- Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013;169:1071-80. [\[Crossref\]](#)
- Phillips EJ, Bigliardi P, Bircher AJ, Broyles A, Chang YS, Chung WH, et al. Controversies in drug allergy: Testing for delayed reactions. *J Allergy Clin Immunol* 2019;143:66-73. [\[Crossref\]](#)
- Calle AM, Aguirre N, Ardila JC, Cardona Villa R. DRESS syndrome: A literature review and treatment algorithm. *World Allergy Organ J* 2023;16:100673. [\[Crossref\]](#)
- Stirton H, Shear NH, Dodiuk-Gad RP. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Drug-Induced Hypersensitivity Syndrome (DiHS)-Readdressing the DRESS. *Biomedicines* 2022;10:999. [\[Crossref\]](#)
- Mansour K, Chadli Z, Ben Fadhel N, Ben Fredj N, Ben Romdhane H, Chaabane A, et al. Antituberculosis-Drugs Induced DRESS: A Multi-drug Hypersensitivity or Drug Hypersensitivity Relapse? A Case Report. *Hosp Pharm* 2024;59:10-4. [\[Crossref\]](#)
- Thein OS, Sutton B, Thickett DR, Parekh D. Mepolizumab rescue therapy for acute pneumonitis secondary to DRESS. *BMJ Case Rep* 2019;12. [\[Crossref\]](#)
- Truong K, Kelly S, Bayly A, Smith A. Successful mepolizumab treatment for DRESS-induced refractory eosinophilic myocarditis and concurrent thyroiditis. *BMJ Case Rep* 2021;14: e242240. [\[Crossref\]](#)
- Kura MM, Hira SK. Reintroducing antituberculosis therapy after Stevens-Johnson syndrome in human immunodeficiency virus-infected patients with tuberculosis: role of desensitization. *Int J Dermatol* 2001;40:481-4. [\[Crossref\]](#)
- Thakur V, Vinay K, Kumar S, Choudhary R, Kumar A, Parsad D, et al. Factors Predicting the Outcome of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A 5-Year Retrospective Study. *Indian Dermatol Online J* 2021;12:258-65. [\[Crossref\]](#)
- Drago F, Cogorno L, Broccolo F, Ciccarese G, Parodi A. A fatal case of DRESS induced by strontium ranelate associated with HHV-7 reactivation. *Osteoporosis Int* 2016;27:1261-4. [\[Crossref\]](#)
- Seishima M, Yamanaka S, Fujisawa T, Tohyama M, Hashimoto K. Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome. *Br J Dermatol* 2006;155:344-9. [\[Crossref\]](#)
- Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P, Rodrigues-Cernadas J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2016;71:1103-34. [\[Crossref\]](#)