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Title

Successful drug desensitization in patients with delayed-type allergic reactions to antituberculosis drugs

Short running title

Antituberculosis drug desensitization

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Highlights

- Success rate of drug desensitization was favorable in non-IgE mediated reaction to antituberculosis drugs.
- The allergic reactions following failed desensitization were generally not severe.
- There was no evidence of clinical drug resistance in the patients who had completed desensitization.
- Desensitization in severe allergic reaction should be carefully conducted with close monitoring.

Abstract

Objective:

To evaluate the outcomes of antituberculosis drug desensitization.

Design:

This was a retrospective study. Inclusion criteria were as follows: age >18 years, documented tuberculosis infection, a previous cutaneous allergic reaction to antituberculosis drugs, and having undergone drug desensitization between January 2003 and March 2014. Definition of allergic reactions to antituberculosis drugs included (1) a

temporal relationship between drug use and allergic reaction; (2) improvement of allergic reaction after drug withdrawal; (3) recurrence of allergic reaction after reintroduction of only the offending drug; and (4) absence of other causes.

Results:

A total of 19 desensitization procedures were performed. The drugs used for these procedures were isoniazid (n = 7), rifampicin (n = 6) or ethambutol (n = 6). Of note, severe allergic reactions (Stevens-Johnson syndrome (n = 4), erythema multiforme (n = 3), and drug rash with eosinophilia and systemic syndrome (n = 1)) were included. All patients underwent resolution of the previous allergic reactions before desensitization. Median duration of desensitization was 18 days. Success rate was 78.9%. The allergic reactions following failed desensitization were not severe; most were maculopapular rashes.

Conclusion:

The desensitization protocol for antituberculosis drugs was associated with high success rate, and the individuals who failed desensitization experienced mild allergic reactions.

Keywords: Desensitization; tuberculosis; antituberculosis; Stevens-Johnson syndrome; rechallenge; allergic reaction; drug allergy; delayedtype

Introduction

Tuberculosis infection is still a significant health problem worldwide. One major challenge in tuberculosis treatment is allergic reactions, which are found in 4-6% of cases (Schaberg et al.,

1996, Small et al., 1991, Tan et al., 2007, Yee et al., 2003). The prevalence of cutaneous allergic reactions to each first-line antituberculous drug is 2-5% for pyrazinamide, 1.2-2% for rifampicin, 1-1.2% for isoniazid and 0.3-1.4% for ethambutol (Schaberg et al., 1996, Tan et al., 2007, Yee et al., 2003).

Patients who have had an allergic reaction to a first-line drug generally receive second-line antituberculous treatment (such as streptomycin or quinolone). However, cutaneous allergic reactions have also been reported for streptomycin and quinolone (Johannes et al., 2007, Lehloeny et al., 2011).

Antituberculous drug desensitization is an optional treatment for patients who have had allergic reactions to antituberculous treatment, especially those who have had allergic reactions to both first-line and second-line antituberculous drugs.

Drug desensitization (or tolerance induction) is defined as a “procedure describing the induction of a clinical tolerance to a drug responsible for previous allergic reaction”. (Scherer et al., 2013) Drug desensitization can be accomplished with the administration of incremental doses of an allergic substance, and it is only indicated in specific situations in which an alternate non-cross-reacting drug cannot be prescribed. (Joint Task Force on Practice et al., 2010) Drug desensitization is generally contraindicated in serious non-IgE-mediated reactions, such as Stevens-Johnson syndrome (SJS). However, it can be carefully performed in patients with a severe non-IgE-mediated reaction (such as SJS) if the benefit of treatment outweighs the risk of a severe reaction. (Joint Task Force on Practice et al., 2010)

There have been several retrospective reports on antituberculous drug desensitization (Buergin et al., 2006, Holland et al., 1990, Horne and Grant, 1963, Kim et al., 2003, Kura and Hira, 2001, Thong et al., 2014). Most of them were case reports describing 1-3 patients (Buergin et al., 2006, Holland et al., 1990, Horne and Grant, 1963, Kim et al., 2003, Kura and Hira, 2001). Thong BY reported that 11 patients underwent sequential desensitization-rechallenge for antituberculosis allergy; however, the report did not show the relationships with the suspected drugs that induced allergic reactions (Thong et al., 2014). The results of tuberculosis treatment after drug desensitization are also important because there was a case report showing that isoniazid resistance may develop during desensitization (Horne and Grant, 1963).

The objective of this study was to describe both the short- and long-term results of antituberculosis drug desensitization.

Methods

Study population

This retrospective cohort study was conducted at both the Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand and Yanhee General Hospital, Bangkok, Thailand. A total of 25 medical records from subjects who had undergone antituberculosis drug desensitization were retrieved from a database and reviewed (Figure 1). The study ended on May 31, 2014.

The inclusion criteria were as follows: (1) age >18 years; (2) presence of a tuberculosis infection, defined as clinical signs and symptoms suggestive of tuberculosis with either a) *Mycobacterium tuberculosis* identified in a clinical specimen (such as via a positive test for acid-fast bacilli (AFB), a molecular assay or culture), or b) signs and symptoms suggestive of tuberculosis improvement after receiving antituberculosis treatment; (3) having had a cutaneous allergic reaction to an antituberculosis drug, with a certain relationship; and (4) having undergone antituberculosis drug desensitization between January 2003 and March 2014. The definition of “certain” allergic reaction to antituberculosis drugs was as follows: (1) temporal relationship between drug use and allergic reaction; (2) improvement of allergic reaction after drug withdrawal or dose reduction; (3) recurrence of allergic reaction after reintroduction of only the offending drug; and (4) absence of other causes. The exclusion criteria were as follows: (1) medical records were destroyed or lost and (2) there was evidence that the subject was not infected with *Mycobacterium tuberculosis*, such as a culture of a clinical specimen revealing atypical mycobacteria.

The study was approved by the Institutional Review Board of Bamrasnaradura Infectious Diseases Institute and the Ethics Committee of Yanhee General Hospital.

Antituberculosis drug desensitization protocol

The desensitization protocol used in this study was modified from a previous report (Kura and Hira, 2001) and an immunotherapy schedule for inhalant immunotherapy (Cox et al., 2011). The principles were as follows: (1) start with a very low initial drug concentration and (2) increase

the drug dose at a low concentration rapidly and at a high concentration slowly, as shown in Table 1.

Pharmacists were responsible for the preparations for drug desensitization. The drug solution for desensitization was stored at 4°C in a refrigerator for less than two days because of drug instability.

Data collection and statistical analysis

All data were collected from medical records, including (1) demographic features, (2) the clinical characteristics of tuberculosis, (3) the clinical features of the allergic reactions to antituberculosis drugs, and (4) the results of tuberculosis treatment.

Default to antituberculosis treatment was defined as stopping antituberculosis drugs for more than two months.

Treatment completion was defined as receiving antituberculosis drugs for an appropriate duration according to tuberculosis guidelines and the decision of the doctor to stop the antituberculosis treatment due to clinical recovery.

The desensitization outcome was classified as a failure if there was an allergic reaction to a drug after drug desensitization or if the patient or doctor decided to stop the antituberculosis drug after desensitization because of a reaction. However, we classified the outcome as an adverse event of desensitization, or “treating through (Scherer et al., 2013)”, if there was an allergic reaction after drug desensitization and the reaction improved without stopping the drug.

The primary outcome was the success rate of antituberculosis drug desensitization, and the secondary outcome was the cure rate of tuberculosis in patients who underwent antituberculosis drug desensitization.

The data were analyzed based on descriptive statistics and non-parametric tests, as appropriate.

All comparisons were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

Participants and baseline demographic features

Figure 1 shows the profile of the study cohort. A total of 13 patients were enrolled, 11 of whom underwent drug desensitization at the Bamrasnaradura Infectious Diseases Institute and 2 of whom underwent drug desensitization at Yanhee General Hospital.

One patient was still receiving antituberculosis treatment at the end of the cohort study. The duration of antituberculosis treatment after drug desensitization was one month for this patient.

The demographic features of the enrolled patients are reported in **Table 2**. Most patients had HIV/AIDS (84.6%). All the 13 enrolled patients were new cases of tuberculosis. Ten patients had clinical signs and symptoms suggestive of tuberculosis, with *Mycobacterium tuberculosis* identified based on clinical specimens, and 3 patients had signs and symptoms suggestive of tuberculosis improvement after receiving antituberculosis treatment. Of note, only two patients had resistance to antituberculosis drugs at baseline. The median (interquartile range (IQR))

duration of receiving combined antituberculosis regimens that included three or more drugs before starting drug desensitization was 36 (22-55) days.

Figure 2 shows details of antituberculosis drug regimens and their adverse events of each patients.

Results of antituberculosis drug desensitization

Figure 1 and 2 shows the results of the desensitization. Among the 13 enrolled patients, 34 antituberculosis drug desensitization procedures were performed. However, we excluded 15 desensitizations because the allergic reactions were not certainly related to the antituberculosis drugs. Ultimately, 19 antituberculosis drug desensitizations were included in the evaluation.

Details of the antituberculosis drug desensitizations are shown in **Table 3**. Notably, previous severe allergic reactions to antituberculosis drugs that were the subject of later desensitization are as follows: Stevens-Johnson syndrome (SJS) (n = 4) or erythema multiforme (EM) (n = 3), and drug rash with eosinophilia and systemic syndrome (DRESS) (n = 1).

Seventy-nine percent of the desensitization procedures were performed with close observation in the specialized ward for tuberculosis in the hospital. All patients underwent clear resolution of the previous allergic reaction before drug desensitization. The median number of steps in the desensitization protocol was 30, and the median duration of desensitization was 18 days (**Table 3**). After desensitization, the drugs that were administered to all patients were the same as those administered in standard practice.

The success rate of desensitization was 78.9%; however, there were 4 cases of failed antituberculosis drug desensitization (isoniazid, n = 2; and ethambutol, n = 2) (**Figure 1, 2**). The allergic reactions that resulted from failed desensitization were not severe. Of the 4 patients who failed drug desensitization, three patients had reactions during outpatient service and decided to stop the drug desensitization when maculopapular rashes occurred. Only one patient failed drug desensitization during hospitalization. This patient had a maculopapular rash and conjunctivitis after receiving ethambutol at 32 milligrams (mg) on the fifth day after starting drug desensitization. The allergic reaction resolved after the patient received ophthalmic medications and oral prednisolone at 0.5 mg/kg of body weight for 5 days. The median (IQR) duration from starting drug desensitization to failing the desensitization was 20 (3-38) days.

The patients who started desensitization with an initial concentration of the drug of 1:100,000 or lower did not fail the desensitization, as shown in **Table 3**.

During antituberculosis drug desensitization, 8 desensitization procedures involved the continuous use of antihistamines, and two desensitization events involved the use of systemic steroids (**Table 3**). The success rate of desensitization with the use of antihistamines or systemic steroids did not differ from that without antihistamine or systemic steroid use (80.0% vs 76.9%, respectively, $p = 1.000$).

Antituberculosis drug desensitization in severe allergic reactions

We defined severe allergic reactions as SJS (n = 4), EM (n = 3) or DRESS (n = 1) (**Table 3, Figure 2**). Seven patients had severe allergic reactions to antituberculosis drugs. Only one of

these patients was not infected with HIV. The offending drugs that induced these severe reactions were isoniazid (n = 2), rifampicin (n = 3), and ethambutol (n = 3).

In a subgroup analysis of the patients with severe allergic reactions (EM/SJS or DRESS, n = 8) and those with mild reactions (maculopapular rash $\pm$ fever, n = 11), the success rate of drug desensitization in patients with severe allergic reactions tended to be lower than that in patients with mild reactions (62.5% vs 86.7%, respectively, $p = 0.297$). The duration of desensitization, the number of steps in the desensitization protocol, and the type of antituberculosis drug were not significantly different between the groups in the subgroup analysis.

Adverse events during desensitization

Five adverse events occurred during drug desensitization. These events were localized maculopapular rashes that occurred approximately 7 days after starting drug desensitization (**Figure 1**).

All the patients who had adverse events during drug desensitization, which were maculopapular rashes, continued the desensitization by decreasing the dose of the drug for at least 3 days or until the rash disappeared and then resumed the desensitization procedure. For example, after one patient developed a maculopapular rash while receiving isoniazid at 100 mg in 10 mL of water, we decreased the concentration of isoniazid to 100 mg in 100 mL of water twice daily until the rash disappeared. When the rash was resolved, we increased the drug concentration again from isoniazid to 100 mg in 100 mL of water to the targeted drug dose as formerly planned. Oral antihistamines could be used during this period, but no patients received systemic steroids to treat these reactions.

Results of antituberculosis treatment

Figure 1 shows the results of antituberculosis treatment after drug desensitization. Of the 13 patients who underwent antituberculosis drug desensitization, 2 patients died approximately 1-2 months after they finished the antituberculosis drug desensitization protocol. These two patients were infected with HIV, were naïve to antiretroviral treatment, and died from PCP and hepatoma.

Ten (76.9%) patients completed antituberculosis treatment and were cured. The median (IQR) duration of antituberculosis treatment after the desensitization of these 10 patients was 10.5 (7.8-13.5) months. There was no clinical evidence of drug-resistant tuberculosis in either the patients who completed antituberculosis treatment (n = 10) or those who died after drug desensitization (n = 2).

Discussion

The drug desensitization of patients who have had a non IgE mediated reaction and have no alternate drug to use can be carefully conducted in the hospital. The success rate in the study was approximately 78.9%, and the success rate of desensitization in the patients who experienced a severe allergic reaction (such as SJS, EM or DRESS) tended to be lower than that in the patients with a mild reaction. Allergic reactions due to the failure of antituberculosis drug desensitization were not severe; most of them were maculopapular rashes. The long-term results

of tuberculosis in the patients who tolerated antituberculosis drug desensitization were excellent, and there was no clinical evidence of drug-resistant tuberculosis.

The patch test was reported to be a diagnostic tool for delayed-type allergic reactions to antituberculosis drugs (Arruti et al., 2016, Goday et al., 1990, Lehloenya et al., 2016, Ozkaya, 2013, Rebollo et al., 2001). The concern about this test is systemic adverse reactions (Lee et al., 2010, Lehloenya et al., 2016), and its result was often drug- and reaction-specific; therefore, a negative result may not be useful (Thong, 2011). The lymphocyte toxicity assay or lymphocyte transformation assay is another diagnostic tool in this situation and was reported previously (Schreiber et al., 1999). Both the patch test and lymphocyte toxicity assay were not available in our hospital during the study period.

According to the guidelines of the American Academy of Allergy, Asthma and Immunology, “For certain conditions (e.g., SJS, TEN, exfoliative dermatitis), desensitization is generally contraindicated, with rare exceptions, such as when the benefit of treatment of a life-threatening illness outweighs the risk of a potentially life-threatening reaction (Joint Task Force on Practice et al., 2010)”. Moreover, there have been reports of desensitization in severe non-IgE-mediated allergic reactions (such as SJS) with antituberculosis drugs (Kura and Hira, 2001, Thong et al., 2014) and other drugs (Douglas et al., 1997, Minor et al., 2012). In this report, the reasons to desensitize patients with severe types of allergic reaction were as follows: (1) there was no alternative available for treatment, as evidenced by second-line antituberculosis drugs (such as streptomycin and ofloxacin) having already been introduced in these patients, followed by later drug-associated allergic reactions; (2) an alternative second-line antituberculosis treatment (such

as ethionamide, p-aminosalicylic acid, or D-cycloserine) was not generally available and was reserved for multidrug-resistant tuberculosis; and (3) desensitization drugs, such as isoniazid and rifampicin, were superior to alternative second-line drugs. Additionally, we reduced the risk of desensitization by close monitoring in the specialized ward for tuberculosis, the desensitization protocol started at very low drug concentrations, and the increase in drug dosing was quite slow compared to other reports (Thong et al., 2014). The success rate of drug desensitization in patients with previous severe drug reactions (such as SJS, EM or DRESS) was 76.9%. Those who failed drug desensitization had only mild allergic reactions, and only one patient had both a maculopapular rash and conjunctivitis.

There is no consensus about using antihistamines or corticosteroids as pre-medications for drug desensitization (Scherer et al., 2013). In the present study, the success rate of the patients who used daily antihistamines or systemic steroids during desensitization did not differ from that of the patients who did not use these treatments. The indications for the use of antihistamines and steroids in these patients are to relieve allergic symptoms from previous drug reactions or from skin diseases, such as pruritic papular eruption (PPE) in HIV-infected patients.

Generally, acquired drug-resistant tuberculosis may occur when (1) there is a period of inadequate antituberculosis regimen use and (2) there is a large population of *Mycobacterium tuberculosis* (such as in pulmonary cavities). Horne NW (Horne and Grant, 1963) described two patients who had pulmonary tuberculosis and developed isoniazid resistance after antituberculosis drug desensitization. However, in the present study, none of the patients who underwent desensitization and completed antituberculosis treatment had any clinical evidence of drug-resistant tuberculosis, possibly because they had already received combined

antituberculosis treatments (which consisted of three or four drugs) for a median of 36 days. In an expert's opinion, if a patient infected with tuberculosis received appropriate combined drug treatment for longer than 2 weeks, the number of infectious organisms would be significantly decreased, and the patient could be non-infectious to other people. In one study, the rate of sputum conversion from positive for AFB to negative in patients infected with pulmonary tuberculosis who received combined antituberculosis treatments was 71% during the first four weeks after drug treatment (Bawri et al., 2008).

Regarding this report, drug desensitization might be an option for tuberculosis-infected patients who have had delayed-type allergic reactions to antituberculosis drugs, especially for those who have already received antituberculosis treatment for at least 2-4 weeks and have no alternative drugs. Antituberculosis drug desensitization could be performed as follows: (a) initial dilution of the drug in sterile water at 1:100,000 or lower; (b) a duration of desensitization of approximately 14 days; (c) hospitalization; and (d) close monitoring for 30-40 days after drug desensitization was completed. If the patient has a mild allergic reaction to the drug (or "treating through" (Scherer et al., 2013)) during desensitization, the dose of the drug should be reduced for at least three days or until the allergic reaction is resolved. Antihistamines can be used to decrease the symptoms of this drug-associated allergic reaction.

Because severe allergic reactions (such as SJS, EM or DRESS) can occur during antituberculosis drug desensitization, patients should be supervised by an allergist and closely monitored in the hospital. Pulmonologists or infectious disease specialists should determine the risks and benefits of desensitization of the culprit drug and design the subsequent

antituberculosis drug regimen and the appropriate duration of treatment before starting desensitization.

The limitations of this study are as follows: (1) causality assessments of allergic reactions to antituberculosis drugs were not included in the *in vivo* or *in vitro* laboratory tests; (2) the data set was incomplete, including limited results of tuberculosis treatment; (3) retrospective data were used; and (4) the desensitization procedure was not validated. These limitations should be carefully considered when interpreting the data.

In conclusion, drug desensitization in patients who had experienced a delayed-type hypersensitivity reaction to antituberculosis drugs was associated with a high success rate. However, mild allergic reactions were found in the cases of failed desensitization.

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Conflict of interest

All authors declare they have no conflicts of interest to disclose.

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References

1. Centers for Disease Control and Prevention. Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR Morb Mortal Wkly Rep 2003; 52 (No. RR-11): [page 68].
2. Fitzgerald DW, Sterling TR, Haas DW, Mycobacterium tuberculosis. In: Mandell GL, Bennett JE, Dolin R, editors. Principle and Practice of Infectious Diseases. 7th ed. Philadelphia, PA: Churchill Livingstone Elsevier Inc; 2010. p. 3129-3163.
3. Nelson HS, Immunotherapy for Inhalant Allergens. In: Adkinson NF, Bochner BS, Yunginger JW, Holgate ST, Busse WW, Simons ER, editors. Middleton's ALLERGY Principle & Practice. 6th ed. Philadelphia, Pennsylvania: Mosby Inc; 2003. p. 1455-1473.
4. Panel on The World Health Organization. Treatment of tuberculosis: guidelines – 4th ed. World Health Organization. Available at <http://www.who.int/tb/en/> Accessed [Feb 24, 2014].
5. Vervloet D, Pradal M, Castelain M. Drug Allergy. Kabi Pharmacia. 1992.
6. World Health Organization (WHO), Uppsala Monitoring Center [internet]. The use of the WHO-UMC system for standardized case causality assessment. Available from: <http://who-umc.org/graphics/4409.pdf>.
7. Arruti N, Villarreal O, Bernedo N, Audicana MT, Velasco M, Uriel O, et al. Positive Allergy Study (Intradermal, Patch, and Lymphocyte Transformation Tests) in a Case of Isoniazid-Induced DRESS. Journal of investigational allergology & clinical immunology 2016;26(2):119-20.
8. Bawri S, Ali S, Phukan C, Tayal B, Baruwa P. A study of sputum conversion in new smear positive pulmonary tuberculosis cases at the monthly intervals of 1, 2 & 3 month under directly observed treatment, short course (dots) regimen. Lung India : official organ of Indian Chest Society 2008;25(3):118-23.
9. Buergin S, Scherer K, Hausermann P, Bircher AJ. Immediate hypersensitivity to rifampicin in 3 patients: diagnostic procedures and induction of clinical tolerance. International archives of allergy and immunology 2006;140(1):20-6.
10. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. The Journal of allergy and clinical immunology 2011;127(1 Suppl):S1-55.
11. Douglas R, Spelman D, Czarny D, O'Hehir RE. Successful desensitization of two patients who previously developed Stevens-Johnson syndrome while receiving trimethoprim-sulfamethoxazole. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 1997;25(6):1480.
12. Goday J, Aguirre A, Diaz-Perez JL. A positive patch test in a pyrazinamide drug eruption. Contact dermatitis 1990;22(3):181-2.
13. Holland CL, Malasky C, Ogunkoya A, Bielory L. Rapid oral desensitization to isoniazid and rifampin. Chest 1990;98(6):1518-9.
14. Horne NW, Grant IW. Development of drug resistance to isoniazid during desensitization: a report of two cases. Tubercle 1963;44:180-2.

15. Johannes CB, Ziyadeh N, Seeger JD, Tucker E, Reiter C, Faich G. Incidence of allergic reactions associated with antibacterial use in a large, managed care organisation. *Drug safety : an international journal of medical toxicology and drug experience* 2007;30(8):705-13.
16. Joint Task Force on Practice P, American Academy of Allergy A, Immunology, American College of Allergy A, Immunology, Joint Council of Allergy A, et al. Drug allergy: an updated practice parameter. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2010;105(4):259-73.
17. Kim JH, Kim HB, Kim BS, Hong SJ. Rapid oral desensitization to isoniazid, rifampin, and ethambutol. *Allergy* 2003;58(6):540-1.
18. Kura MM, Hira SK. Reintroducing antituberculosis therapy after Stevens-Johnson syndrome in human immunodeficiency virus-infected patients with tuberculosis: role of desensitization. *International journal of dermatology* 2001;40(7):481-4.
19. Lee SW, Yoon NB, Park SM, Lee SM, Um SJ, Lee SK, et al. Antituberculosis drug-induced drug rash with eosinophilia and systemic symptoms syndrome confirmed by patch testing. *Journal of investigational allergology & clinical immunology* 2010;20(7):631-2.
20. Lehloenyia RJ, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2011;15(12):1649-57.
21. Lehloenyia RJ, Todd G, Wallace J, Ngwanya MR, Muloiwa R, Dheda K. Diagnostic patch testing following tuberculosis-associated cutaneous adverse drug reactions induces systemic reactions in HIV-infected persons. *The British journal of dermatology* 2016;175(1):150-6.
22. Minor DR, Rodvien R, Kashani-Sabet M. Successful desensitization in a case of Stevens-Johnson syndrome due to vemurafenib. *Melanoma research* 2012;22(5):410-1.
23. Ozkaya E. Eczematous-type multiple drug allergy from isoniazid and ethambutol with positive patch test results. *Cutis* 2013;92(3):121-4.
24. Rebollo S, Sanchez P, Vega JM, Sedano E, Sanchis ME, Asensio T, et al. Hypersensitivity syndrome from isoniazid with positive patch test. *Contact dermatitis* 2001;45(5):306.
25. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *The European respiratory journal* 1996;9(10):2026-30.
26. Scherer K, Brockow K, Aberer W, Gooi JH, Demoly P, Romano A, et al. Desensitization in delayed drug hypersensitivity reactions -- an EAACI position paper of the Drug Allergy Interest Group. *Allergy* 2013;68(7):844-52.
27. Schreiber J, Zissel G, Greinert U, Schlaak M, Muller-Quernheim J. Lymphocyte transformation test for the evaluation of adverse effects of antituberculous drugs. *European journal of medical research* 1999;4(2):67-71.

28. Small PM, Schecter GF, Goodman PC, Sande MA, Chaisson RE, Hopewell PC. Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. *The New England journal of medicine* 1991;324(5):289-94.
29. Tan WC, Ong CK, Kang SC, Razak MA. Two years review of cutaneous adverse drug reaction from first line anti-tuberculous drugs. *The Medical journal of Malaysia* 2007;62(2):143-6.
30. Thong BY. Clinical applications of drug desensitization in the Asia-Pacific region. *Asia Pacific allergy* 2011;1(1):2-11.
31. Thong BY, Chia FL, Tan SC, Tan TC, Leong KP, Tan JW, et al. A retrospective study on sequential desensitization-rechallenge for antituberculosis drug allergy. *Asia Pacific allergy* 2014;4(3):156-63.
32. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *American journal of respiratory and critical care medicine* 2003;167(11):1472-7.

Figure legends

Figure 1

Figure1. Study cohort of the enrolled patients

AE, adverse event; CMV, cytomegalovirus; IQR, interquartile range; MP, maculopapular; PCP, *Pneumocystis carinii* pneumonia or *Pneumocystis jiroveci* pneumonia;

- ^a Median duration from receiving antituberculosis drug regimen to starting desensitization was 72 (IQR 57-145) days. However, median duration of receiving three or more antituberculosis drugs was 36 (IQR 22-55) days.
- ^b defined as follows: (1) time relationships between drug use and allergic reaction; (2) improvement of allergic reaction after drug withdrawal or dose reduction; (3) recurrence of allergic reaction after reintroduction of only the offending drug; and (4) Absence of other causes¹⁵
- ^c of the 13 patients enrolled, 9 patients underwent desensitization for one antituberculosis drug; 3 patients, for two antituberculosis drugs; and one patient, for two antituberculosis drugs and re-desensitized them again because of desensitization failure
- ^d defined as an allergic reaction that appeared after drug desensitization and improved without stopping the drug desensitization
- ^e defined as an allergic reaction that appeared during or after drug desensitization and that caused the patient or doctor to decide to stop the drug
- ^f defined as stopping antituberculosis drugs for more than two months
- ^g defined as receiving antituberculosis drugs for an appropriate duration according to current tuberculosis guidelines, with a doctor deciding to stop the antituberculosis treatment due to clinical recovery

Figure 2

Figure 2: Details of each enrolled patient about antituberculosis drugs that were prescribed before and after desensitization.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, Ciprofloxacin; DRESS, drug reaction with eosinophilia and systemic syndrome; E, Ethambutol; EM, erythema multiforme; GrC, graded challenge; I, Isoniazid; L, Levofloxacin; MP, maculopapular rash; O, Ofloxacin; R, Rifampicin; S, Streptomycin; SJS, Stevens-Johnson syndrome; Z, Pyrazinamide

^ascale for measuring duration on diagram of each patient, it is equal to 30 days.

^b defined as follows: (1) time relationships between drug use and allergic reaction; (2) improvement of allergic reaction after drug withdrawal or dose reduction; (3) recurrence of allergic reaction after reintroduction of only the offending drug; and (4) Absence of other causes¹⁵

^cname of antituberculosis drugs that were desensitized in each subject. For example, subject No.1 received desensitization for isoniazid, ethambutol and ofloxacin, respectively.

^d defined as an allergic reaction that appeared after drug desensitization and improved without stopping the drug desensitization

^ethe subject No.4 had maculopapular rash after starting ethambutol desensitization for eight days, however the rash was disappeared later by reducing drug concentration and using oral antihistamine (treating trough). After finishing the ethambutol desensitization for four days (day 26th), he had maculopapular rash and he stopped ethambutol by himself at home. After the rash disappeared, his primary doctor prescribed him for isoniazid, rifampicin, and pyrazinamide, respectively, by graded challenge. He received these antituberculosis drugs for 6 months without allergic reaction.

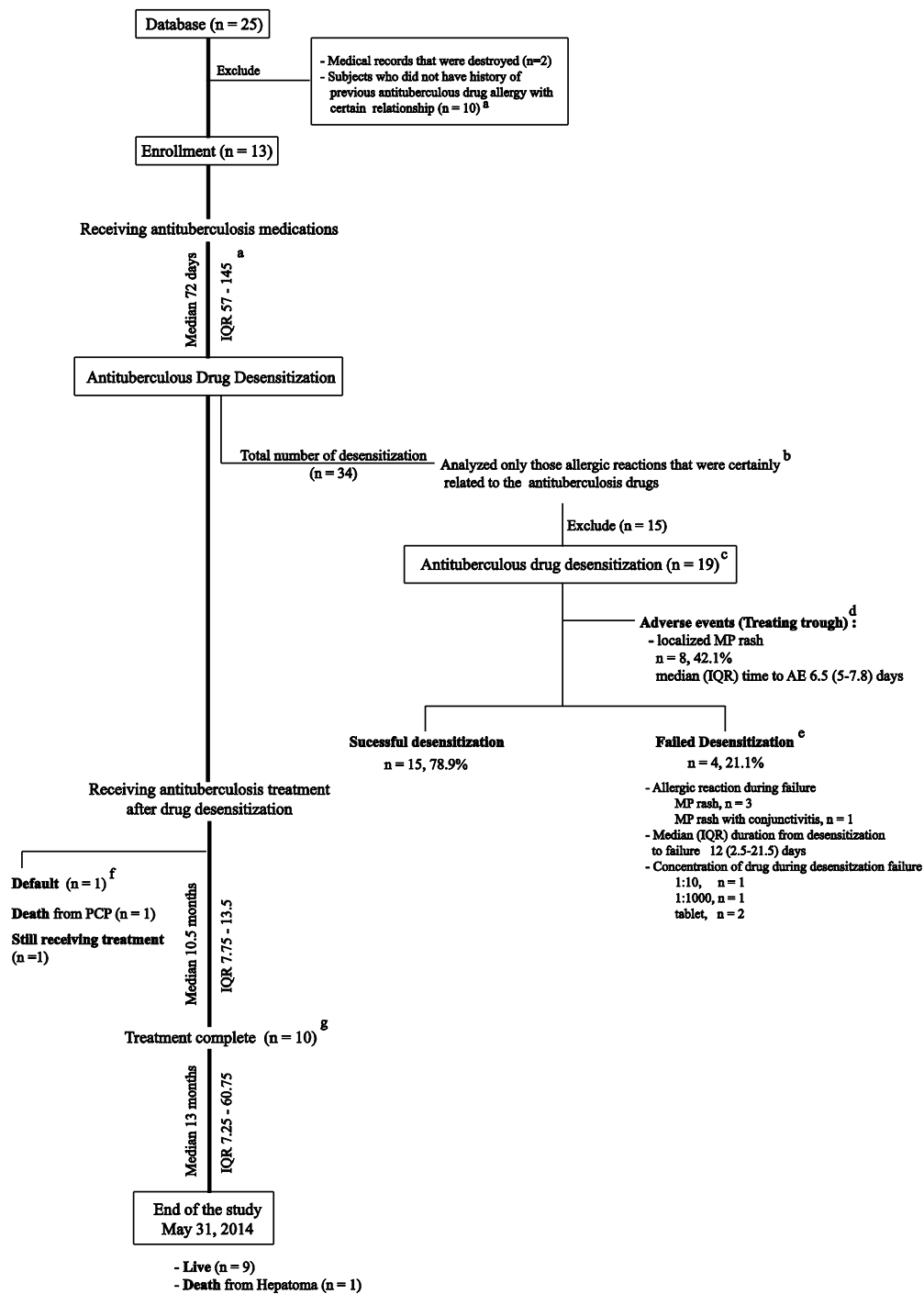


Table 1 Example of a successful rifampicin desensitization protocol in a patient who had SJS due to rifampicin ^a.

Day from start	Time	Dose (mg)	Preparation
Day 1	9:00 am	0.0003	1 cc of RFP 300 mg (tablet) in water 1,000,000 cc
	6:00 pm	0.0009	3 cc of RFP 300 mg (tablet) in water 1,000,000 cc
Day 2	9:00 am	0.003	1 cc of RFP 300 mg (tablet) in water 100,000 cc
	6:00 pm	0.009	3 cc of RFP 300 mg (tablet) in water 100,000 cc
Day 3	9:00 am	0.03	1 cc of RFP 300 mg (tablet) in water 10,000 cc
	6:00 pm	0.09	3 cc of RFP 300 mg (tablet) in water 10,000 cc
Day 4	9:00 am	0.3	1 cc of RFP 300 mg (tablet) in water 1,000 cc
	6:00 pm	0.9	3 cc of RFP 300 mg (tablet) in water 1,000 cc
Day 5	9:00 am	3	1 cc of RFP 300 mg (tablet) in water 100 cc
	6:00 pm	6	2 cc of RFP 300 mg (tablet) in water 100 cc
Day 6	9:00 am	12	4 cc of RFP 300 mg (tablet) in water 100 cc
	6:00 pm	24	8 cc of RFP 300 mg (tablet) in water 100 cc
Day 7	9:00 am	30	1 cc of RFP 300 mg (tablet) in water 10 cc
	6:00 pm	60	2 cc of RFP 300 mg (tablet) in water 10 cc
Day 8	9:00 am	90	3 cc of RFP 300 mg (tablet) in water 10 cc
	6:00 pm	120	4 cc of RFP 300 mg (tablet) in water 10 cc
Day 9	9:00 am	150	5 cc of RFP 300 mg (tablet) in water 10 cc
	6:00 pm	180	6 cc of RFP 300 mg (tablet) in water 10 cc
Day 10	9:00 am	210	7 cc of RFP 300 mg (tablet) in water 10 cc
	6:00 pm	240	8 cc of RFP 300 mg (tablet) in water 10 cc
Day 11	9:00 am	240	8 cc of RFP 300 mg (tablet) in water 10 cc
	6:00 pm	240	8 cc of RFP 300 mg (tablet) in water 10 cc
Day 12-13	9:00 am	300	1 tablet of RFP 300 mg (tablet)
Day 14	9:00 am	450	1 tablet of RFP 450 mg (tablet)

RFP, rifampicin; SJS, Stevens-Johnson syndrome

^a protocols for ethambutol and isoniazid desensitization were generally done with the same manner like this example. The important keys are as follows: (1) starting at very low concentration (about dilute one tablet of the drug into 10,000 to 10,000,000 mL of water according to previous allergic reaction); (2) increase the drug dose rapidly at a low concentration and slowly at a high concentration; and (3) keep the diluted drug at 4°C and use it within two days.

Table 2 Baseline demographic features before drug desensitization (n = 13)

Demographic features	Results
Median (IQR) age, years	43 (35-50)
Male sex, n (%)	9 (69.2%)
HIV positive, n (%)	11 (84.6%)
- Median (IQR) baseline CD4 cell count (cell/ μ L)	104 (26-308)
- Antiretroviral treatment, n (%)	1 (9.1%)
Tuberculosis manifestations	
New case	13 (100%)
Site of infection	
- Pulmonary, n (%)	6 (46.2%)
- Extrapulmonary, n (%)	2(15.4%)
- Disseminated, n (%)	5 (38.5%)
Result of mycobacterial sensitivity testing	
- Resistance to a low concentration of INH, n (%)	1 (7.7%)
- Resistance to streptomycin, n (%)	1 (7.7%)
Baseline laboratory characteristics	
HBsAg positive, n (%)	1 (7.7%)
Anti HCV positive, n (%)	2(15.4%)
Median (IQR) hematocrit, %	37 (33-41)
Median (IQR) creatinine, mg/dL	0.7 (0.6-0.9)
Median (IQR) AST, U/ μ L	28 (18-34)
Median (IQR) ALT, U/ μ L	36 (19-51)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INH, isoniazid; IQR, interquartile range; HBsAg, hepatitis B surface antigen, HCV, hepatitis C virus

Table 3 Details of antituberculous drug desensitization (n = 19)

Details		Overall	Desensitization Outcome	
			Success	Failure ^a
Drugs for desensitization				
- INH, n (%)		7 (36.8%)	5	2
- RFP, n (%)		6 (31.6%)	6	0
- EMB, n (%)		6 (31.6%)	4	2
Previous allergic reaction to drugs for desensitization				
- MP rash ± fever, n (%)		11 (57.9%)	10	1
- EM, n (%)		3 (15.8%)	2	1
- SJS, n (%)		4 (21.1%)	2	2
- DRESS, n (%)		1 (5.3%)	1	0
HIV status				
- Anti HIV positive		17 (89.5%)	13	4
- Anti HIV negative		2 (10.5%)	2	0
Median (IQR) duration of desensitization, days		18 (14-21)	18 (14-22)	11 (3.5-19)
Median (IQR) steps of desensitization protocol, n		30 (25-33)	31 (25-37)	20 (7-30)
Frequency of desensitization per day				
- Twice per day, n (%)		19 (100%)	15	4
Hospitalization ^b , n (%)		15 (78.9%)	13	2
Median (IQR) of the initial concentration of each drug, x 10 ⁻³ mg				
- INH		5.0 (0.3-10.0)	NA	NA
- RFP		4.5 (0.2-45)	NA	NA
- EMB		40 (28-40)	NA	NA

Initial dilution of the drug in sterile water ^c			
- 1:10,000,000, n (%)	1 (5.3%)	1	0
- 1:1,000,000, n (%)	3 (15.8%)	3	0
- 1:100,000, n (%)	4 (21.4%)	4	0
- 1:10,000, n (%)	10 (52.6%)	6	4
- 1:1,000, n (%)	1 (5.3%)	1	0
Antihistamine use			
- Continuous ^d , n (%)	8 (42.1%)	6	2
- As needed, n (%)	3 (15.8%)	3	0
Systemic steroid use ^e , n (%)	2 (10.5%)	2	0

DRESS, drug rash with eosinophilia and systemic syndrome; EM, erythema multiforme; EMB, ethambutol; INH, isoniazid; IQR, interquartile range; MP, maculopapular; RFP, rifampicin; SJS, Stevens-Johnson syndrome

^a The desensitization outcome was classified as a failure if there was an allergic reaction to a drug after drug desensitization and if the patient or doctor decided to stop the antituberculosis drug after desensitization because of the reaction.

^b The reason of hospitalization was to closely monitor patients during drug desensitization

^c Initial dilution of desensitization drug in the tablet form in sterile water, e.g., INH, 100 mg/tablet; RFP, 300 or 450 mg/tablet; and EMB, 400 mg/tablet

^d indications for the use of antihistamine continuously were to relieve allergic symptoms from skin diseases, such as pruritic papular eruption (PPE) in HIV-infected patients

^e indication for the use of systemic steroids in these patients was to relieve allergic symptoms from previous drug reactions