



Efficacy and tolerability of desensitization in the treatment of delayed drug hypersensitivities to anti-tuberculosis medications

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ABSTRACT

Background: Delayed drug hypersensitivity to first-line anti-tuberculosis medication is a major challenge in tuberculosis treatment.

Objective: This study was performed to investigate the efficacy/tolerability of desensitization therapy in treatment of first-line anti-tuberculosis medication hypersensitivity and the usefulness of immunologic evaluation therein.

Methods: This study was conducted as a prospective, observational cohort study. Subjects who experienced hypersensitivity reactions, including maculopapular exanthema (MPE) and drug reaction with eosinophilia and systemic symptoms (DRESS), to first-line anti-tuberculosis medications (isoniazid [INH], ethambutol [EMB], rifampin [RFP], and pyrazinamide [PZA]) were enrolled. Patch, intradermal, lymphocyte transformation, and oral provocation tests were performed to determine culprit drugs, which were desensitized with rapid and graded challenge protocols. Breakthrough reactions (BTRs) during or after desensitization were assessed.

Results: In total, 31 desensitization treatments (INH, 8; EMB, 8; RFP, 11; PZA, 4) to 12 patients (8 with MPE and 4 with DRESS) were performed. The overall success rate of desensitization was 80.7%. All the study subjects except one completed the full course of anti-tuberculosis treatment. The overall BTR free rate was 64.5%. Sixteen (80%) treatments for MPE and four (36.4%) for DRESS were BTR free ($P = 0.023$). Drugs that were positive on any two of three immunologic studies showed significantly high BTR rates ($P = 0.014$), although this was not correlated with desensitization failure rate.

Conclusion: Rapid desensitization therapy to multiple anti-tuberculosis medications for delayed drug hypersensitivity was safe and successful. Combination of multiple immunologic evaluations may predict BTR although it needs validation in larger studies.

1. Introduction

The worldwide incidence of tuberculosis in 2017 was 133 per 100,000 population, with mortality reported at 1.3 million deaths among HIV-negative people and 300,000 deaths among HIV-positive people, according to the World Health Organization's 2018 Global

Tuberculosis report [1]. South Korea ranks at the top in tuberculosis incidence among the member countries of the Organization for Economic Cooperation and Development. For the Korean population, studies have reported adverse drug reactions leading to permanent discontinuation of first-line anti-tuberculosis medications in 2.5–9.7% [2,3] and second-line medication in 16% [3]. Drug reaction with

Abbreviations: BTR, breakthrough reaction; DRESS, drug reaction with eosinophilia and systemic symptoms; EMB, ethambutol; IM, intramuscular injection; INH, isoniazid; IV, intravenous injection; LTT, lymphocyte transformation test; MPE, maculopapular exanthema; PZA, pyrazinamide; RFP, rifampin; SCAR, severe cutaneous adverse reaction; SI_{max}, maximum stimulation index

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eosinophilia and systemic symptoms (DRESS) to anti-tuberculosis medication was reported in 0.7% of all tuberculosis patients, leading to interruption in treatment for a prolonged period and changes in treatment regimen to a second-line anti-tuberculosis medication [4]. In tuberculosis treatment, regimens containing second-line medications are known to be more toxic and less effective than those with first-line agents. Therefore, desensitization for delayed drug hypersensitivity to anti-tuberculosis medications may be a more effective treatment option than changing the regimen to a second-line one. However, despite being shown to be safe and successful in certain situations, desensitization for delayed drug hypersensitivity has been less extensively studied than that for immediate drug hypersensitivity [5].

Skin tests for delayed drug hypersensitivity have been shown to have low sensitivity and specificity, limiting the role in determining culprit drugs [5,6]. Moreover, desensitization in cases with a positive skin test has been suggested to be more dangerous than that in cases with a negative skin test [5]. No study, however, has compared the success rate or breakthrough reaction (BTR) rate of desensitization according to positivity on skin tests for delayed drug hypersensitivities to anti-tuberculosis medications.

In the present study, we performed a prospective, observational cohort study designed to investigate the usefulness of immunologic evaluation and the efficacy/tolerability of desensitization in the treatment of first-line anti-tuberculosis medication hypersensitivity.

2. Materials and methods

2.1. Subjects

Subjects who showed culture positivity for *Mycobacterium tuberculosis* and experienced hypersensitivity reactions, including maculopapular exanthema (MPE) and DRESS, to first-line anti-tuberculosis medication, such as isoniazid (INH), ethambutol (EMB), rifampin (RFP), or pyrazinamide (PZA), were enrolled in the present study. DRESS was defined as the presence of fever, skin rash, hematologic abnormalities (eosinophilia, atypical lymphocytosis), and systemic organ involvement. The scoring system for DRESS postulated by RegiSCAR network was used [7]. Following RegiSCAR, cases were classified as follows: > 5, definite case; 4–5, probable case; 2–3, possible case; or < 2 no case [7]. In the present study, definite, probable, and possible cases were classified as DRESS.

2.2. Immunologic evaluation to determine culprit drugs

After recovery from hypersensitivity reactions, immunologic evaluations were performed to assess the culprit drugs. Patch tests were performed using 10% commercial drug powder in white petrolatum. The results were read on days 2 and 4 according to the guidelines of the International Contact Dermatitis Research Group [8]. Intradermal tests were conducted by applying 0.1, 1, and 5 mg/mL of anti-tuberculosis medication and were read 20 min after and on day 2 to assess delayed responses. Intradermal tests were considered positive when the diameter of wheals were larger than 3 mm or increased in size compared to the initial bleb [9]. Lymphocyte transformation test (LTT) was performed using peripheral blood mononuclear cells in the recovery stage as previously reported [10–12]. The LTT results were considered positive if the maximum stimulation index (SI_{max}) was the same or higher than 2.

2.3. Desensitization protocol

Tables 1 and 2 presents the protocols of rapid desensitization and graded challenge. Desensitization to culprit drugs was started one after another at 3-day intervals via an oral route in a ward admission setting. In cases with BTRs, the intervals for next drug desensitization were adjusted according to responses to treatment of BTRs. The sequence of

desensitization was determined by the potential of the drugs to cause drug hypersensitivity. Desensitization protocols were developed starting from the initial dose with 1/600 (INH, and RFP), 1/300 (PZA), and 1/1000 (EMB) of full dose in solution formula with 5% dextrose water. Two concentrations of solution formula for each drug were prepared by pharmacists (INH, 0.5 and 5 mg/mL; EMB, 0.8 and 8 mg/mL; RFP, 1 and 5 mg/mL; PZA, 5 and 10 mg/mL). The dose of each step was doubled at 15-min intervals with antihistamine premedication. A total of nine (INH, RFP, and PZA) to 10 (EMB) steps of rapid desensitization were undertaken. In certain cases with mild MPE who showed less allergic reaction to immunologic tests and refused to be admitted in a ward (11 desensitizations in 5 patients), graded challenge was applied. Graded challenge was started from about 1/6 of full dose and gradually increased by doubling doses in three steps over 1 day (INH, 50, 100, and 150 mg; EMB, 125, 275, and 400 mg; RFP, 100, 200, and 300 mg; PZA, 250, 450, and 800 mg). All of the subjects provided written informed consent, and the study protocol was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MBR-OBS-15-219).

2.4. Breakthrough reaction (BTRs)

BTRs during or after desensitization were divided into three grades according to international guidelines [13]. Desensitization was planned to be immediately stopped and BTRs were treated according to the given grade (grade 1, antihistamines equivalent to 20 mg of loratadine; grade 2, antihistamines, methyl prednisolone 62.5 mg intravenous injection (IV), and salbutamol inhalation; and grade 3, epinephrine 0.5 mg intramuscular injection (IM), antihistamines, methyl prednisolone 62.5 mg IV, and salbutamol inhalation) in modification of a previous report [14]. The decision for further continuation of anti-tuberculosis drug treatment in the presence of BTR was dependent on the response to treatment of BTRs. When a BTR was observed during the desensitization course, the dose of drug was decreased to the previous step prior to which the BTR occurred. Full drug dose was continued to be administered with the treatment medication when a grade 1 BTR occurred after the desensitization course finished.

2.5. Statistical analysis

Data for continuous variables were compared using the Mann–Whitney *U* test, and Fisher's exact test was used for categorical variables. All computations were performed using SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA). GraphPad Prism 5.0 software (GraphPad Inc., San Diego, CA, USA) was used for the production of graphs.

3. Results

3.1. Baseline clinical characteristics and clinical outcomes of the study subjects

In total, 12 subjects of ages from 30 to 80 years old (53.8 ± 17.3) underwent desensitization. Eight (66.7%) subjects were females. Drug susceptibility tests for *Mycobacterium tuberculosis* revealed sensitivity to first-line anti-tuberculosis medications. Eight patients (66.7%) exhibited MPE; the others experienced DRESS. Clinical characteristics, immunologic evaluations, treatment options, and outcomes for each subject are presented in Table 3. Table 4 presents the clinical characteristics and total scores on RegiSCAR in subjects with DRESS. Two possible and two probable cases of DRESS were enrolled.

The most common culprit drug was RFP (12 subjects) followed by INH (9 subjects), EMB (9 subjects), and PZA (7 subjects). The overall positive rate for all immunologic studies, including patch and intradermal tests and LTT, of culprit drugs was 59.5%. A total of five (13.5%), 16 (43.2%), and 12 (32.4%) tests of 37 culprit drugs was

Table 1
Protocols of rapid desensitization.

Step	Time from start (min)	Isoniazid		Ethambutol		Rifampin		Pyrazinamide	
		Administration dose (mg)	Cumulative dose (mg)	Administration dose (mg)	Cumulative dose (mg)	Administration dose (mg)	Cumulative dose (mg)	Administration dose (mg)	Cumulative dose (mg)
1	0	0.5	0.5	0.8	0.8	1	1	5	5
2	15	1	1.5	1.6	2.4	2	3	10	15
3	30	2	3.5	3.2	5.6	5	8	20	35
4	45	4	7.5	6.4	12	10	18	30	65
5	60	8.5	16	12.8	24.8	20	38	60	125
6	75	15	31	32	56.8	40	78	100	225
7	90	35	66	50	106.8	70	148	200	425
8	105	75	141	96	202.8	150	298	400	825
9	120	160	301	200	402.8	300	598	800	1625
10	135			400	802.8				

positive in patch tests, intradermal tests, and LTT, respectively. Ten of 37 culprit drugs showed positivity on two or more immunologic studies. The mean latent period until the appearance of adverse reactions was 17.50 ± 18.97 days. The mean interval between the disappearance of adverse reactions and the initiation of desensitization was 25.3 ± 17.3 days.

All study subjects except one completed the full course of anti-tuberculosis treatment without development of drug resistant tuberculosis. One subject who could not complete the full course of treatment was not tolerable to anti-tuberculosis medication because of old age and poor general condition. Six subjects completed the course with the first-line anti-tuberculosis medication, and others completed with a mixture of first- and second-line anti-tuberculosis medications.

3.2. Factors related with successful desensitization treatment to anti-tuberculosis medications

Among all 31 desensitization treatments, 25 (80.7%) treatments were successful. The success rates of each drug were as follows: INH, 6 (75%); EMB, 7 (87.5%); RFP, 8 (72.7%); and PZA, 4 (100%). Eighteen (90%) treatments for MPE and seven (63.6%) treatments for DRESS were successful. Fourteen (77.8%) treatments with a rapid desensitization protocol and 10 (90.9%) treatments with graded challenge were successful. Neither the kinds of anti-tuberculosis medication, clinical manifestation of drug hypersensitivity, nor type of desensitization protocol affected the success rate of desensitization (Table 5).

Among the desensitization success group ($n = 25$), two (10.5%) drugs were positive on patch tests, and 10 (50%) were positive on intradermal tests. In the desensitization failure group ($n = 6$), two (66.7%) drugs showed positivity on patch tests, and four (66.7%) drugs showed positivity on intradermal tests. The mean SI_{max} of LTT was 2.1 ± 1.5 in the success group, while that in the failure group was 2.1 ± 0.7 . No single immunologic evaluation was significantly different between the desensitization success and failure groups (Table 5). The success rates of desensitization therapy in cases with triple negativity, single positivity, and double positivity on three immunologic

studies were 92.3%, 80%, and 62.5% ($P > 0.05$ for all) (Fig. 1).

No significant differences in the mean SI_{max} of LTT for each anti-tuberculosis drug were observed between the desensitization success and failure groups (Fig. 2). The number of patients with a positive response on patch and intradermal tests and LTT (defined as an $SI_{max} \geq 2$) for each drug showed no significant differences between the two groups.

3.3. Factors related with BTRs during and after desensitization

Among all 31 desensitization treatments, 20 (64.5%) showed no BTRs. The BTR free rates of each drug were as follows: INH, 5 (62.5%); EMB, 6 (75%); RFP, 5 (45.5%); and PZA, 4 (100%). Sixteen (80%) treatments for MPE and four (36.4%) treatments for DRESS were BTR free ($P = 0.023$). Ten (50%) treatments with a rapid desensitization protocol and 10 (90.9%) treatments with graded challenge were BTR free ($P = 0.047$). The kinds of anti-tuberculosis medications did not affect the BTR free rate of desensitization.

The grades of BTRs were grade 1 in all cases. Among the 11 desensitization treatments with BTRs, five (45.5%) maintained the anti-tuberculosis drug with additive antihistamine medications. In all of the 11 desensitization treatments with BTRs, the BTRs developed after the desensitization course finished. Five (45.5%) BTRs were observed within the first day, another five were on the second day, and one on the third day.

Among the desensitization treatments with BTRs ($n = 11$), two (28.6%) drugs were positive on patch tests and 10 (72.7%) drugs were positive on intradermal tests. The mean SI of LTT was 2.1 ± 0.6 for drugs with BTR, while for BTR-free drugs was 2.1 ± 1.7 . No single immunologic evaluation was associated with the presence of BTRs. Also, no significant differences in the mean SI_{max} of each anti-tuberculosis drug on LTT were observed between cases with and without BTRs (INH, 2.0 ± 0.9 vs. 3.1 ± 3.3 ; EMB, 1.9 ± 0.5 vs. 1.5 ± 0.4 ; RFP, 2.2 ± 0.6 vs. 2.1 ± 0.5 ; PZA, 1.5 ± 0.2 , $P > 0.05$ for all). The BTR-free rates of desensitization therapy in cases with triple negativity, single positivity, and double positivity on three immunologic studies

Table 2
Protocols of graded challenge.

Day	Step	Time from start (hour)	Administration dose (mg)			
			Isoniazid	Ethambutol	Rifampin	Pyrazinamide
1 day (Outpatient clinic)	1	0	50	125	100	250
	2	1	100	275	200	450
	3	2	150	400	300	800
	4	3	Discharge	Discharge	Discharge	Discharge
2 day (At home)	5	0	100	300	200	500
	6	6	200	500	400	1000
3 day (At home)	7	0	300	800	600	1500

Table 3
Clinical characteristics and treatment option of total study subjects.

Case	Age/ gender	Clinical diagnosis of tuberculosis	Clinical diagnosis of adverse drug reaction	Culprit drugs	Evaluation	Desensitization protocol and success or failure												Treatment regimen of tuberculosis	Final outcome
						OPT positive drugs		Lymphocyte transformation test (SI _{max})											
						Patch test	Intradermal test	INH	EMB	RFP	PZA	INH	EMB	RFP	PZA				
1	35/F	Tbc pleurisy	DRESS	HERZ	HER	(-)	HRZ		8.0	1.0	1.5	1.5	RS	RS	RS	RS	HERZ	Completion	
2	43/F	Tbc lymphadenitis	DRESS	HERZ	HE	H	HRZ		3.1	2.2	2.3	2.5	RF	RS	RS	ND	ER	Completion	
3	52/M	Pul. tuberculosis	MPE	HERZ	HEZ	(-)	R		1.6	1.8	2.4	1.8	GS	GS	GS	GS	HERZ	Completion	
4	52/F	Tbc colitis	MPE	HER	HER	NA	R		1.2	1.4	2.4	1.7	GS	RS	RS	ND	HER	Completion	
5	76/F	Pul. tuberculosis	MPE	HERZ	REZ	(-)	HR		1.7	1.7	1.7	1.5	GS	GS	ND	GS	HEZ, moxifloxacin	Completion	
6	65/M	Pul. tuberculosis	MPE	HR	HR	(-)	HR		1.4	1.8	2.5	1.9	RS	ND	GF	ND	HEZ, moxifloxacin	Completion	
7	69/M	Pul. tuberculosis	DRESS	HERZ, SM	HERZ	EZ	R		3	1.5	3	3.3	ND	RF	RS	ND	R, azithromycin	Completion	
8	80/M	Pul. tuberculosis	DRESS	HERZ	HERZ	NA	R		1.6	1.4	2.2	1.7	RF	ND	RF	ND	Stopped	Completion	
9	30/F	Pul. tuberculosis	MPE	R	R	NA	R		1.7	1.6	1.5	1.3	ND	ND	RF	ND	HEZ + moxifloxacin	Completion	
10	38/F	Pul. tuberculosis	MPE	RZ	RZ	RZ	NA		1.7	1.6	1.5	1.3	ND	ND	RS	RS	HEZ + moxifloxacin	Completion	
11	38/F	Pul. tuberculosis	DRESS	HER	HER	NA	NA		NA	NA	NA	NA	RS	RS	GS	ND	HER	Completion	
12	68/F	Tbc clitis	MPE	ER	ER	(-)	R		NA	NA	NA	NA	ND	GS	RS	ND	ER	Completion	

OPT, oral provocation test; SI_{max}, maximum stimulation index; INH (H), isoniazid; EMB (E), ethambutol; RFP (R), rifampin; PZA (Z), pyrazinamide; Tbc, tuberculosis; DRESS, drug reaction with eosinophilia and systemic symptoms; RS, rapid desensitization success; RF, rapid desensitization failure; ND, not done; Pul., pulmonary; MPE, maculopapular rash; (–), negative; GS, graded challenge success; NA, not available; GF, graded challenge failure; SM, streptomycin.

were 92.3%, 50%, and 37.5% (Fig. 3). Cases that were positive on at least one immunologic study showed significantly higher BTR rates than cases that were triple negative ($P = 0.014$ for triple negative vs. double positive, $P = 0.008$ for triple negative vs. single and double positive).

4. Discussion

In the present study, the overall success rate of desensitization treatment for anti-tuberculosis medication was 80.7%. Success rates did not significantly differ according to the types of medications, clinical manifestations of drug hypersensitivity, and type of desensitization protocol. In a previous study, we suggested that INH- and RFP-specific T cell activation was a possible mechanism of MPE and DRESS induced by anti-tuberculosis medications [10]. The overall rate of positivity on immunologic studies and the study subjects was 59.5%: positivity was defined as having at least one positive response on skin tests and LTT against anti-tuberculosis medications. However, immunologic evaluation was unable to predict the success of desensitization therapy.

Multiple drugs are prescribed to treat tuberculosis at the same time, and all of them hold the potential to cause drug hypersensitivity. In clinical practice, confirmation of culprit drugs is challenging, which is ascribed to low sensitivity and specificity of skin tests and LTT. Therefore, studies regarding desensitization therapy to multiple anti-tuberculosis medications are important. This is the first case series study to describe successful desensitization therapy for multiple anti-tuberculosis medications with rapid desensitization protocols. So far, no controlled studies and no recommended protocols on desensitization have been reported for delayed-type hypersensitivity to anti-tuberculosis medication. Most of the studies that are available were case reports [15–18]; a few were case series of 10–46 patients with slow [19–21] and rapid protocols [22]. The overall success rate of desensitization therapy to anti-tuberculosis medication was 78.2% in a study of single drug desensitization with slow protocol [19]. Others reported success rates of 78.9% and 92% in studies of multiple drug desensitization with slow protocols [20,21]. Another study [22] that performed rapid desensitization to a single drug for 10 subjects reported a 100% success rate of desensitization. Two successful cases with rapid desensitization to multiple anti-tuberculosis drugs were also reported [15,18]. Consistent with previous studies, we observed an overall success rate of 80.7% for desensitization, a rate that was not inferior to that for a slow desensitization protocol or single drug desensitization. Taking into account therapeutic duration and compliance, especially for multiple drug hypersensitivity cases, we suggest that application of a rapid protocol prior to a slow protocol should be considered.

Studies regarding the tolerability of desensitization therapy to anti-tuberculosis hypersensitivity are scanty. Overall BTR rates were reported at 54.5% and 42.1% in previous studies [20,21] with a slow desensitization protocol to multiple drugs [18,19] and 40% in a study with a rapid desensitization protocol to a single anti-tuberculosis drug [20]. Most of the BTRs were mild and tolerable with additive antihistamines [18,21,22] or systemic steroids [15,22]. In the present study, 36.7% of the desensitization treatments elicited BTRs that were mild and well controlled with antihistamines, similar to previous desensitization studies with slow [20,21] and rapid protocols [22]. Although the BTR rates of desensitization for delayed drug hypersensitivities were higher than that for immediate drug hypersensitivities (6–26%) [14,23], the severity of the reported BTRs was relatively low. Taken together, BTRs were mild and tolerable with additive antihistamines, indicating that desensitization therapy is safe for treating delayed drug hypersensitivity to anti-tuberculosis medications.

Desensitization to severe cutaneous adverse reaction (SCAR) was not recommended in a previous position paper [5]. Several reports performed desensitization to anti-tuberculosis medication in cases with DRESS and Stevens-Johnson syndrome [20,21], with a reported success rate of 62.5% [21]. In the present study, four subjects with DRESS were

Table 4
Clinical features of study subjects with DRESS.

Case	Age/gender	RegiSCAR score	Skin rash extent (> 50%)	Fever	Peripheral eosinophil count (/uL)	AST/ALT (IU/ L)	Organ involvement		Days to be fully resolved (≥ 15 days)
							Liver	Kidney	
1	35/F	5	Yes	Yes	520	265/166	Yes	No	Yes
2	43/F	3	Yes	No	1600	22/20	No	No	Yes
7	69/M	4	Yes	Yes	2930	21/14	No	No	Yes
8	80/M	2	Yes	No	2500	25/17	No	Yes	No

DRESS, drug reaction with eosinophilia and systemic symptoms; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 5
Immunologic findings and desensitization protocol according to the success of desensitization.

Clinical characteristics	Success group (n = 25)	Failure group (n = 6)	P value
Desensitization drug			
INH	6	2	
EMB	7	1	
RFP	8	3	
PZA	4	0	
Clinical diagnosis of adverse drug reaction			
MPE	18	2	0.151
DRESS	7	4	
Patch test			
Positive	2	2	0.073
Negative	17	1	
Not available	6	3	
Intradermal test			
Positive	10	4	0.652
Negative	10	2	
Not available	5	0	
Lymphocyte transformation test (SI_{max})	2.06 ± 1.48	2.06 ± 0.65	0.358
Desensitization protocol			
Rapid	15	5	0.383
Graded	10	1	

Continuous data are presented as mean $\pm$ SD. Dichotomous data are presented as number (%). Data were analyzed by Mann whitney analysis and Fisher's exact test.

INH, isoniazid; EMB, ethambutol; RFP, rifampin; PZA, pyrazinamide; MPE, maculopapular exanthema; DRESS, drug reaction with eosinophilia and systemic symptoms; SI_{max} , maximum stimulation index; SD, standard deviation.

included, and 63.6% of desensitization treatments therein were successful, consistent with the aforementioned study [21]. The success rates of desensitization for SCAR tended to be lower than those for MPE, although statistical significance was not observed in either the present or previous study [21]. Meanwhile, BTR rates appeared to differ according to the initial clinical diagnosis of adverse drug reactions. The previous study [21] reported that 100% of SCARs (DRESS, erythema multiforme, Stevens-Johnson syndrome) showed BTRs during desensitization, while only 27.2% for MPEs showed BTRs. Consistent with the previous study, 63.6% of desensitizations for DRESS and 20% of MPE elicited BTRs in the present study. Taken together, although BTR rates were significantly high, desensitization success rates were not significantly low in cases initially presenting with SCAR. Therefore, desensitization to anti-tuberculosis medication in cases with SCAR, such as DRESS, under careful monitoring can be a safe therapeutic option.

Although the mechanism of desensitization on delayed type hypersensitivities is not well established, drug specific T cell activation has been suggested to be involved in anti-tuberculosis medication hypersensitivity [10]. In the present study, intradermal and patch tests, as well as LTT, were performed to evaluate the culprit drugs and their relationships with success and BTR rates. In previous studies [20–22], immunologic studies have not been documented [20–22] or have been used only to judge the causative drugs [19]. In the present study, no single immunologic study was related with success or BTR rate,

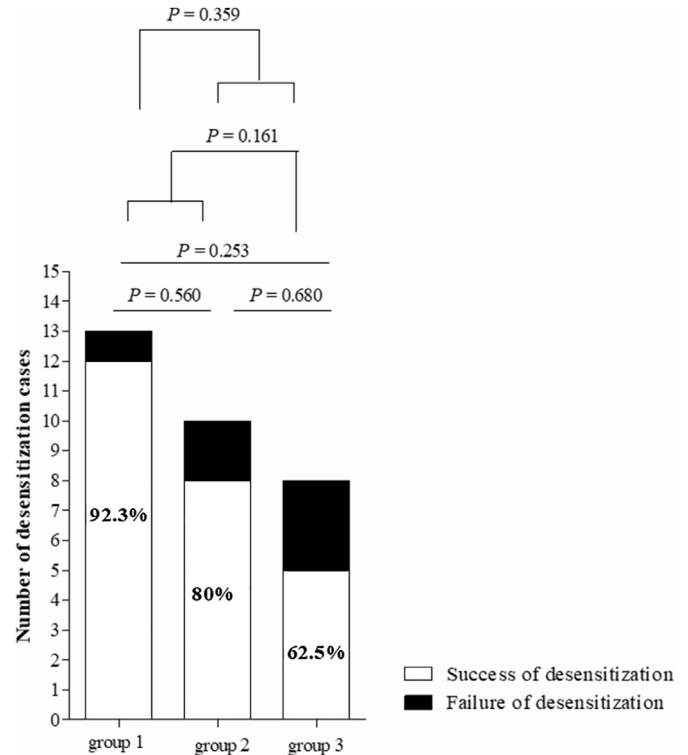


Fig. 1. Number of desensitization cases with success according to the number of positive immunologic evaluation.

There were no significant differences in number of success cases according to the number of positive immunologic evaluation. Group 1, desensitization cases that showed triple negative to immunologic evaluation; group 2, desensitization cases that showed single positive to immunologic evaluation; group 3, desensitization cases that showed double positive to immunologic evaluation. Patch test, intradermal test and lymphocyte transformation test were performed for each culprit drug. BTR, breakthrough reaction. Data were analyzed by Fisher's exact test.

consistent with previous studies. However, drugs that were double positive on any two of three immunologic studies showed significantly higher BTR rates, but were unrelated with desensitization failure rate. These findings suggest that a combination of multiple immunologic evaluations may predict BTR during or after desensitization therapy and may help with selecting subjects who require intensive monitoring.

The present study has several limitations. Immunologic evaluations were not entirely performed in all subjects, and the number of subjects enrolled was not enough to confirm the effectiveness of desensitization therapy for patients with anti-tuberculosis medication hypersensitivity. Further studies with a larger number of subjects undergoing all immunologic tests are warranted.

5. Conclusion

In conclusion, rapid desensitization therapy to multiple anti-

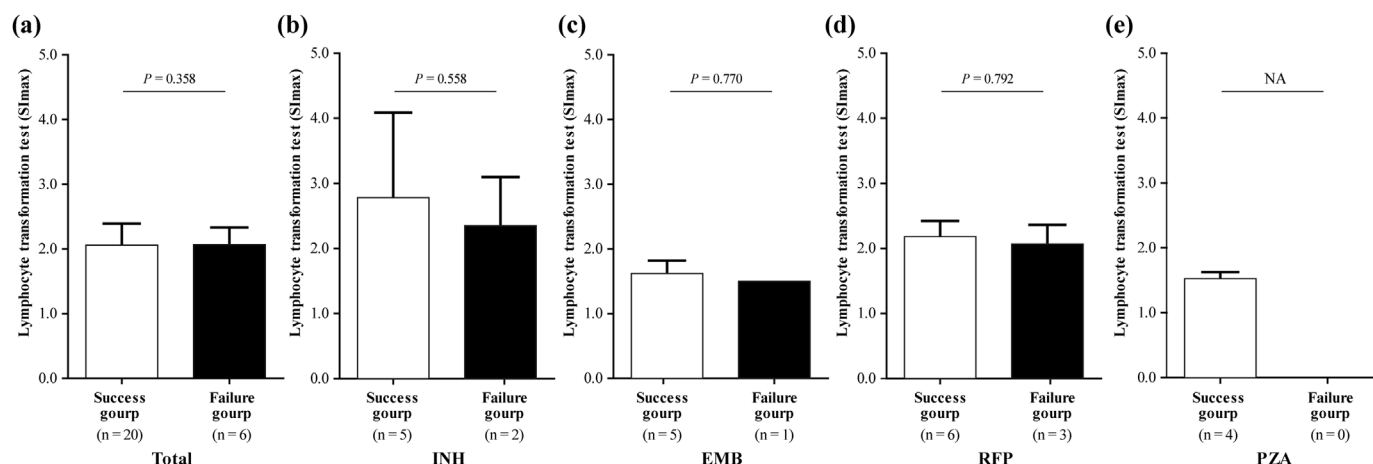


Fig. 2. Comparison of LTT between success and failure group in each anti-tuberculosis drug. LTT results of desensitization caused to all anti-tuberculosis drugs (a), to INH (b) to EMB (c) to RFP (d), and to PZA (e). No significant differences in the mean SI of LTT of for each anti-tuberculosis drug were observed between the desensitization success and failure groups. Data were analyzed by Mann whitney analysis. INH, isoniazid; EMB, ethambutol; RFP, rifampin; PZA, pyrazinamide; SI_{max}, maximum stimulation index; LTT, lymphocyte transformation test.

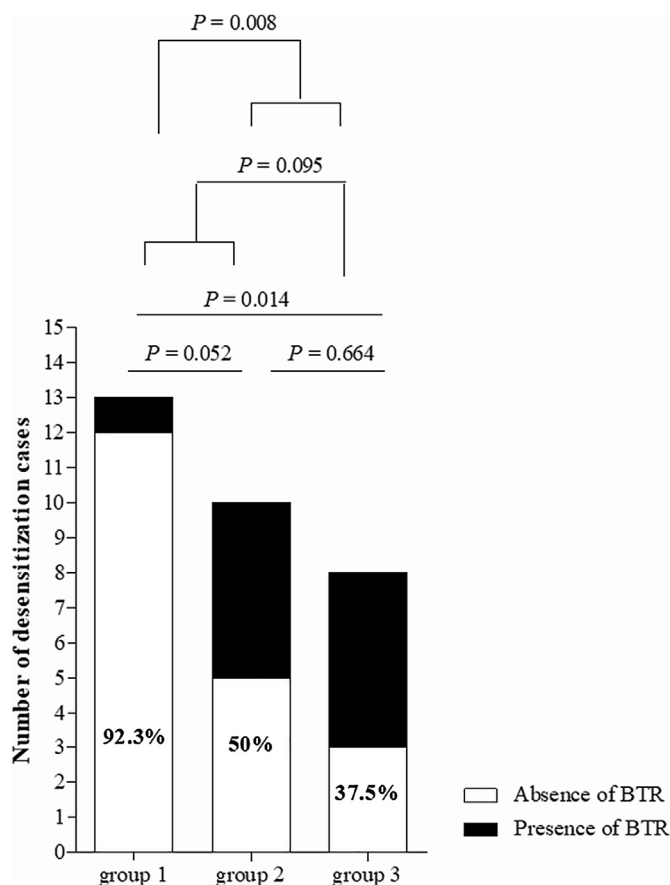


Fig. 3. Number of desensitization cases without BTRs according to the number of positive immunologic evaluation.

Cases that were positive on at least one immunologic study showed significantly higher BTR rates than cases that were triple negative ($P = 0.008$). Cases that were double positive on immunologic studies showed significantly higher BTR rates than cases that were triple negative ($P = 0.014$). Group 1, desensitization cases that showed triple negative to immunologic evaluation; group 2, desensitization cases that showed single positive to immunologic evaluation; group 3, desensitization cases that showed double positive to immunologic evaluation. Patch test, intradermal test and lymphocyte transformation test were performed for each culprit drug. BTR, breakthrough reaction. Data were analyzed by Fisher's exact test.

tuberculosis medications for delayed drug hypersensitivity was found to be safe and successful although it needs validation in larger studies. Given the advantages of first-line anti-tuberculosis medications in regards to safety and efficacy, we suggest that desensitization therapy can be an effective therapeutic option for patients with anti-tuberculosis medication hypersensitivity who would otherwise have to change to a second-line medication.

Declarations of interest

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