

Desensitization Therapy for Allergic Reactions to Antituberculous Drugs

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Abstract

Objective We retrospectively evaluated the clinical usefulness of desensitization therapy for many patients showing allergic reactions to anti-mycobacterial drugs (INH and RFP) according to the proposition reported by the Japanese Society for Tuberculosis (JST).

Methods Desensitization therapy for anti-mycobacterial drugs was performed according to the propositions of JST for forty-six patients with mycobacterial disease in several hospitals participating in the Chugoku-Shikoku Mycobacterial Disease Committee between January 1999 and December 2009.

Results Adverse reactions occurred as drug-induced skin eruptions in 23 patients, drug-induced fever in 16, and drug-induced fever plus eruption in 7. The causative drugs suggested by the clinical course or DLST were RFP in 30 patients and INH in 16. The clinical effects of desensitization therapy for individual drugs was good in 23 of 30 patients (77%) receiving RFP, and in 13 of 16 (81%) receiving INH. Ten patients showing failure of desensitization included 5 elderly patients and 2 patients with a history of drug allergies. The interval until initiation of desensitization therapy ranged from 5 to 30 days after the disappearance of adverse reactions and the interval until the appearance of adverse reactions during desensitization therapy ranged from 3 to 18 days. A comparative study between the patient group with successful desensitization therapy and that with failure of desensitization did not show any significant differences except for the interval until initiation of desensitization therapy.

Conclusion We confirmed the clinical effectiveness of desensitization therapy for anti-mycobacterial drugs according to the propositions of JST in this multicenter study.

Key words: anti-mycobacterial drugs, desensitization therapy, adverse reaction

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Introduction

We sometimes encounter patients in whom we must discontinue the administration of anti-mycobacterial drugs because of adverse reactions such as drug-induced fever or drug-induced skin eruptions. Although new anti-mycobacterial drugs have recently been developed to replace isoniazid (INH) or rifampicin (RFP) for these patients, these new anti-mycobacterial drugs have not yet been commercialized. Therefore, desensitization therapy for anti-

mycobacterial drugs remains an important approach to managing allergic reactions. The propositions for desensitization therapy for patients showing allergic reactions to anti-mycobacterial drugs (INH and RFP) were proposed by the Japanese Society for Tuberculosis (JST) in 1997 (1). However, there are few reports describing desensitization therapy for anti-mycobacterial drugs in Japan (2, 3) or in western countries (4).

In this multicenter study, we retrospectively evaluated the clinical usefulness of desensitization therapy for many cases showing allergic reactions to anti-mycobacterial drugs (INH

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Table 1. Desensitization Therapy for Isoniazid (INH) and Rifampicin (RFP)

		INH	RFP
Day	1	25(mg)	25(mg)
	2	25	25
	3	25	25
	4	50	50
	5	50	50
	6	50	50
	7	100	100
	8	100	100
	9	100	100
	10	200	200
	11	200	200
	12	200	200
	13	300	300
	14	300	300
	15	300	300
	16	400	450

(Japanese Society for Tuberculosis, 1997)

and RFP) according to the propositions reported by JST in order to confirm the effectiveness of this desensitization therapy.

Materials and Methods

The subjects consisted of 46 patients with mycobacterial disease who underwent desensitization therapy for anti-mycobacterial drugs (INH and RFP) between January 1999 and December 2009 in five hospitals participating in the Chugoku-Shikoku Mycobacterial Disease Committee. Desensitization therapy was routinely performed according to the propositions (1) reported by JST in all patients in participating hospitals (Table 1) who had shown allergic reactions such as drug-induced fever or drug-induced skin eruptions during anti-mycobacterial treatment (INH or RFP). After the causative drug was determined, desensitization therapy was initiated for that drug. We retrospectively investigated the clinical findings including initial anti-mycobacterial treatment, interval until the appearance of adverse reactions, causative drugs suggested, interval until initiation of desensitization therapy, interval until the appearance of adverse reactions during desensitization therapy and outcome. There were no constant criteria used to predetermine the interval until the initiation of desensitization therapy after the appearance of adverse events, but rather we depended on the judgment of the attending physicians to determine the appropriate timing. We suspected the causative drugs based on the clinical course of the patient as judged by the attending physician and/or the result of drug lymphocyte stimulation test (DLST).

Statistical analysis

Data were input using Excel 2000 (Microsoft) and then transferred to Santa Software, version 7.0, for statistical analysis. Pearson's χ^2 test was used to compare data from the two groups and McNemar's test was used to compare

paired data. Mann-whitney U test was used to compare unpaired data. Differences showing a probability 0.05 were considered significant.

Results

Forty-six patients who underwent desensitization therapy ranged from 23 to 88 years old (mean age: 60 years old) and consisted of 25 males and 21 females. Seven patients (15%) had a past history of drug allergy. The underlying disease was pulmonary tuberculosis (TB) in 28 patients, pulmonary nontuberculous mycobacterial (NTM) disease in 11, tuberculous lymphadenopathy in 3, TB pleuritis in 3, and pulmonary TB plus TB lymphangitis in one. The regimen of anti-mycobacterial treatment was INH+RFP+ethambutol (EB)+pyrazinamide (PZA) in 16 patients, INH+RFP+EB in 11, INH+RFP+streptomycin (SM) in 3, INH+RFP in 1, and RFP+EB+clarithromycin (CAM)+SM in 11. Adverse reactions to anti-mycobacterial therapy consisted of 23 patients with drug-induced skin eruptions, 16 with drug-induced fever, 7 with drug-induced fever plus skin eruptions.

Regarding the relationship between causative drugs and adverse reactions, RFP was suggested to be the causative drug in 30 patients (15 patients based on both clinical course and DLST and 15 patients based on the clinical course alone). The specific adverse reactions due to RFP were drug-induced skin eruptions in 15, drug-induced fever in 11, drug-induced fever plus skin eruptions in 4. INH was suggested to be the causative drug in 16 patients (9 patients based on both clinical course and DLST and 7 patients based on the clinical course alone). The adverse reactions due to INH were drug-induced skin eruptions in 8, drug-induced fever in 5, drug-induced fever plus skin eruptions in 3.

While the clinical effect of desensitization therapy for RFP was good in 23 of 30 patients (77%) and poor in 7 of 30 patients (23%), that for INH was good in 13 of 16 patients (81%) and poor in 3 of 16 patients (19%) following treatment according to the JST guidelines.

The clinical findings in cases of failed desensitization therapy for RFP (7 patients) and INH (3 patients) are shown in Table 2, 3. Among ten patients showing a failure of desensitization, 5 were elderly patients and two had a past history of drug allergy. The interval until initiation of desensitization therapy ranged from 5 to 30 days (mean: 15.6 days) after the disappearance of adverse reactions and the interval until appearance of adverse reactions during desensitization therapy ranged from 3 to 18 days (mean: 10.9 days). The final outcomes of these failed cases were discontinuation of the causative drug in all cases and levofloxacin (LVFX) was administered instead of the causative drug in three of ten patients. Although a second course of desensitization therapy was performed in one case, repeated therapy was not successful either.

Finally, we compared the clinical findings between the patient group that successfully achieved desensitization and

Table 2. Clinical Findings of Cases Showing Failure of Desensitization Therapy for RFP (7 Cases)

Case	Age, Sex	History of drug allergy	Clinical diagnosis	Anti-mycobacterial drugs	Adverse reaction	Interval until appearance of adverse reaction	Interval until initiation of desensitization therapy	Adverse reaction during desensitization therapy	Interval until appearance of adverse reaction during desensitization therapy	Outcome
1	75, F	(—)	Pulmonary TB	INH RFP EB	Fever + Eruption	1 day after treatment	30 days after adverse reaction	Fever + Eruption	15 days after treatment	Stopped, INH+EB Continued
2	68, F	(—)	Pulmonary NTM	RFP EB CAM SM	Eruption	3 days after treatment	10 days after adverse reaction	Eruption	12 days after treatment	Stopped, Change to LVFX
3	75, F	(—)	Pulmonary TB	INH RFP	Fever	7 days after treatment	21 days after adverse reaction	Fever	9 days after treatment	Stopped, INH+EB Continued
4	43, M	(+)(NSAID)	Pulmonary TB	INH RFP EB PZA	Eruption	3 days after treatment	14 days after adverse reaction	Eruption	11 days after treatment	Stopped, INH+EB Continued
5	52, M	(—)	Pulmonary NTM	RFP EB CAM SM	Eruption	4 days after treatment	5 days after adverse reaction	Eruption	9 days after treatment	Stopped, Change to LVFX
6	88, M	(—)	TB pleuritis	INH RFP EB	Fever	5 days after treatment	20 days after adverse reaction	Fever	18 days after treatment	Stopped, INH+EB Continued
7	48, M	(—)	Pulmonary TB	INH RFP EB PZA	Eruption	3 days after treatment	12 days after adverse reaction	Eruption	10 days after treatment	Stopped, INH+EB Continued

TB : Tuberculosis, NIM : Nontuberculous mycobacteriosis, INH : isoniazid, RFP : rifampicin, EB : ethambutol, SM : streptomycin, PZA : pyrazinamide, CAM : clarithromycin, LVFX : levofloxacin

Table 3. Clinical Findings of Cases Showing Failure of Desensitization Therapy for INH (3 Cases)

Case	Age, Sex	History of drug allergy	Clinical diagnosis	Anti-mycobacterial drugs	Adverse reaction	Interval of appearance of adverse reaction	Interval until Initiation of desensitization therapy	Adverse reaction during desensitization therapy	Interval until appearance of adverse reaction during desensitization therapy	Outcome
1	52,F	(+)(^{PIPC} NSAID)	Pulmonary TB +TB pleuritis	INH RFP EB PZA	Eruption	2 days after treatment	10 days after Adverse reaction	Eruption	3 days after treatment	Stopped, Second desensitization therapy, Failure
2	38,F	(-)	Pulmonary TB	INH RFP EB PZA	Fever + Eruption	7 days after treatment	14 days after Adverse reaction	Eruption	12 days after treatment	Stopped, RFP+EB Continued
3	76,M	(-)	Pulmonary TB	INH RFP EB	Fever	5 days after treatment	20 days after Adverse reaction	Fever	10 days after treatment	Stopped, RFP+EB Continued

TB : Tuberculosis, INH : isoniazid, RFP : rifampicin, EB : ethambutol, SM : streptomycin, PZA : pyrazinamide, CAM : Clarithromycin, LVFX : levofloxacin

that showing failure of desensitization. These findings are summarized in Table 4. Although the interval until initiation of desensitization therapy after the disappearance of adverse reactions was significantly shorter in the group showing failure of desensitization than that in the successful group, there were no significant differences in other clinical findings.

Discussion

Since PZA has been included in the initial standard therapy for anti-mycobacterial treatment, the frequency of adverse reactions to anti-mycobacterial drugs has been re-

ported to range between 20 and 50% (5-7). Because standard therapy for anti-mycobacterial treatment consists of three or four anti-mycobacterial drugs in combination, it is difficult to identify the causative drug when adverse allergic reaction appears. Although we performed drug lymphocyte stimulation test (DLST) or leukocyte migration inhibition test (LMIT) at that time, all cases were judged on the clinical course because of the low positive response rate on these tests. When we encountered such reactions, we discontinued the suspected causative drug and changed to another anti-mycobacterial drug. However, because there are few anti-mycobacterial drugs that can replace INH or RFP to date,

Table 4. The Comparison between the Patient Group Showing Successful Desensitization and That Showing Failure of Desensitization

Clinical characteristics	Success group (n=36)	Failure group (n=10)	p-value
Age (Mean $\pm$ S.D.)	59.6 $\pm$ 10.8	61.5 $\pm$ 10.2	0.565
Gender (Male : Female)	20 :16	5:5	0.382
History of drug allergy	5(13.9%)	2(20.0%)	0.145
Clinical diagnosis			
TB disease	27(75.0%)	8(80.0%)	0.666
NTM disease	9(25.0%)	2(20.0%)	0.670
Adverse reaction			
Drug eruption	18(50.0%)	5(50.0%)	0.998
Drug fever	13(36.1%)	3(30.0%)	0.560
Drug fever+ eruption	4(11.1%)	2(20.0%)	0.078
Causative drugs			
RFP	23(63.9%)	7(70.0%)	0.545
INH	13(36.1%)	3(30.0%)	0.564
Interval until appearance of adverse reaction (days)	4.8 $\pm$ 0.6	4.0 $\pm$ 0.5	0.095
Interval until initiation of desensitization therapy (days)	27.2 $\pm$ 1.8	15.6 $\pm$ 1.2	0.012
Interval until appearance of adverse reaction during desensitization therapy (days)	15.2 $\pm$ 1.1	10.9 $\pm$ 0.8	0.086

TB:Tuberculosis, NTM:Nontuberculous mycobacteriosis, RFP:rifampicin, INH:isoniazid

desensitization therapy for INH or RFP remains important. Although INH and/or RFP were suspected to be causative drugs in ten cases, we evaluated the clinical usefulness of desensitization therapy for patients in whom desensitization therapy was performed for the most strongly suspected causative drugs in this study in order to avoid interactions between the two drugs.

Concerning the protocol of desensitization therapy for anti-mycobacterial drugs, there are propositions for desensitization therapy that have been proposed by JST (1), but there are few reports investigating desensitization therapy in Japan (1, 8) or in western countries (9, 10). We performed desensitization therapy according to the propositions reported by JST in all patients included in this study. There is a big difference in the protocol of desensitization therapy for anti-mycobacterial drugs between JST and that in previous reports from western countries. While the initial dose of INH or RFP starts at 25 mg/day and is gradually increased every three days over a period of more than two weeks in the desensitization therapy proposed by JST, that in the west starts from 0.1 mg every 45 minutes and requires only two days to complete desensitization therapy according to previous reports. With respect to timing between doses, the protocol in western countries was modified with respect to timing between doses from that used for penicillin (11, 12). Although the clinical effect of the protocol in western countries showed a good result in six of ten cases (60%) (10), our protocol showed better results of 77% (RFP) and 81% (INH), respectively. We consider that a wide interval of administration is important for anti-mycobacterial drugs that

have longer pharmacokinetics such as INH or RFP.

We obtained good results with a 77-81% success rate for INH and RFP in this study. However, ten patients failed desensitization therapy. Regarding the causes of failure, we compared findings between the successful desensitization group and the failed desensitization group. Although there were no significant differences in background factors such as age, gender or drug allergy history or interval until appearance of adverse reactions, or interval until the appearance of adverse reactions during desensitization therapy, successful desensitization therapy was significantly more frequently achieved in patients showing a longer interval between desensitization therapy and the discontinuation of anti-mycobacterial treatment. In the future, we would like to try a lower starting dose (for example; 1 mg/day) and slower rate of increase (every one week) during desensitization therapy for anti-mycobacterial drugs.

Concerning the speculation regarding the drug causing the allergic reaction, JST indicated that desensitization therapy should be initiated after the causative drugs using DLST or LMST have been identified whenever possible. However, it was difficult to identify the drug causing the allergic reaction because positive findings on DLST were comparatively low (56% for RFP and 50% for INH). Because other reports also indicated that DLST shows positive results in only 40% of cases even when the causative drug is tested (13), it is not easy to identify the causative drug by DLST alone. Therefore, we speculated on the causative drug based on the clinical course of the patient in all patients, referring to the judgment of the attending physician for each patient.

There are a few limitations in this study. First, although we performed this study according to the propositions of JST, we should also perform a large scale study including several countries because there is no gold standard for desensitization therapy for anti-mycobacterial drugs in western countries. We have to determine the protocol for desensitization therapy of anti-mycobacterial drugs that would be most appropriate in the future. Secondly, there is a question of whether the method of determining the causative drug is appropriate because it was speculated from the clinical course recorded by attending physicians and/or the result of DLST.

Although new anti-mycobacterial drugs such as nitroimidazole derivatives (OPC-67673, PA-824) (14, 15) and new quinolone antibiotics (R207910) (16) that show strong in vitro efficacy have recently been developed, these drugs have not yet been commercialized. Therefore, anti-mycobacterial drugs such as INH or RFP are still necessary for anti-mycobacterial treatment. We could confirm the clinical usefulness of the desensitization therapy according to the propositions of JST from the good effectiveness for many patients as far as possible through this multicenter study as well as in the previous study (4). Because the frequency of adverse reactions due to anti-mycobacterial drugs is high compared to that of other drugs, it is important to develop a careful desensitization therapy for anti-mycobacterial treatment considering not only the desensitization therapy according to JST proposition but also investigating a protocol of slowly increasing the doses of anti-mycobacterial drugs.

References

1. Japanese Society for Tuberculosis. Desensitization therapy of anti-tuberculous drugs. *Kekkaku* **72**: 697-700, 1997 (in Japanese).
2. Kobashi Y, Okimoto N, Matsushima T, et al. Desensitization therapy for antituberculous drugs. *Kekkaku* **75**: 521-526, 2000 (in Japanese).
3. Kobashi Y, Okimoto N, Matsushima T, et al. Desensitization therapy for allergic reactions of antituberculous drugs. *Kekkaku* **75**: 699-704, 2000 (in Japanese).
4. Matz J, Borish LC, Routes JM, et al. Oral desensitization to rifampicin and ethambutol in mycobacterial disease. *Am J Respir Crit Care Med* **149**: 815-817, 1994.
5. Holland CL, Malasky C, Ogunkoya A, et al. Rapid oral desensitization to isoniazid and rifampin. *Chest* **98**: 1518-1519, 1990.
6. Centers for Disease Control and Prevention (CDC), American Thoracic Society. Update: adverse event data revised American Thoracic Society/CDC recommendations against the use of rifampicin and pyrazinamide for treatment of latent tuberculosis infection-United States, 2003. *MMWR Morb Mortal Wkly Rep* **52**: 735-739, 2003.
7. Schaberg T, Rebhan K, Lode H, et al. Risk factor for side-effects of isoniazid, rifampicin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *Eur Respir J* **9**: 2026-2030, 1996.
8. Kobashi Y, Niki Y, Kawane H, et al. Adverse reactions of antituberculous agents. *Kekkaku* **73**: 485-490, 1998 (in Japanese).
9. Holland CL, Malasky C, Ogunkoya A, Bielory L. Rapid oral desensitization to isoniazid and rifampin. *Chest* **98**: 1518-1519, 1990.
10. Matz J, Borish LC, Routes JM, Rosenwasser LJ. Oral desensitization to rifampin and ethambutol in mycobacterial disease. *Am J Respir Crit Care Med* **149**: 815-817, 1994.
11. Borish L, Tamir R, Rosenwasser LJ. Intravenous desensitization to beta-lactam antibiotics. *J Allergy Clin Immunol* **80**: 314-319, 1987.
12. Wendel GD, Stark BJ, Jamison RB, et al. Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med* **312**: 1229-1232, 1985.
13. Schreiber J, Zissel G, Greinert U, et al. Lymphocyte transformation test for the evaluation of adverse effects of antituberculous drugs. *Eur J Med Res* **4**: 67-71, 1999.
14. Hurdle JG, Lee RB, Budha NR, et al. A microbiological assessment of novel nitrofuranylamides as anti-tuberculosis agents. *J Antimicrob Chemother* **62**: 1037-1045, 2008.
15. Stover CK, Phan XQ, Erwin AL, et al. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. *Nature* **405**: 962-966, 2000.
16. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* **307**: 223-227, 2005.