

A retrospective study on sequential desensitization-rechallenge for antituberculosis drug allergy

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Background: Antituberculosis (anti-TB) drug allergy often involves multiple concurrently administered drugs which subsequently need to be reinitiated as no better alternatives exist.

Objective: To describe the results of tailored sequential desensitization-rechallenge (D-R) for anti-TB drug allergy.

Methods: Consecutive patients who had undergone D-R to anti-TB drugs between 1 September 1997 and 31 January 2012 were recruited. Following resolution of the acute reaction, anti-TB drug was restarted at 1:6,000 to 1:3 of the final daily dose (FDD), with gradual single or multiple step daily dose escalation to the FDD. Subsequent drugs were sequentially added ≥ 3 days later when the preceding drug was tolerated. Full blood count and liver function tests were monitored prior to addition of each new drug.

Results: There were 11 patients of whom 10 were male, predominantly Chinese (8 patients). Regimens comprised at least 3 drugs: isoniazid (INH), rifampicin (RIF), ethambutol (EMB), pyrazinamide (PZA), or streptomycin. All patients had nonimmediate reactions, with cutaneous eruptions, where maculopapular exanthema (MPE) was the most common (8 patients). Drug-induced hypersensitivity syndrome (DIHS) occurred in 6 patients, and Stevens Johnson syndrome (SJS) in 2 patients. D-R to INH was successful in 7/9 patients (77.8%) and to RIF/EMB/PZA/streptomycin in all. Of the 2 patients who failed INH D-R, 1 developed fever and MPE on day 3, the other MPE on day 8. D-R with INH and RIF respectively was successful in 2 patients with SJS. Among DIHS patients, 1 failed D-R with INH (fever and MPE on day 3). There were 23/25 (92%) successful D-R among the 11 patients. All patients completed TB treatment of ≥ 5 months' duration with no cases of drug-resistant TB.

Conclusion: Tailored sequential TB drug D-R is successful where no better alternative therapies are available, with careful dose escalation and close monitoring, and after a careful risk-benefit assessment.

Key words: Allergy; Desensitization; Drug eruptions; Drug hypersensitivity syndrome

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INTRODUCTION

Mycobacterium tuberculosis infection remains endemic in Asia, in particular in China and India [1]. The World Health Organization (WHO) estimates that there are approximately 8.8 million new cases of tuberculosis (TB) and 1.6 million deaths from TB annually. In Singapore, the incidence rate of TB is 40 cases per 100,000 resident population, with 3% of new TB cases with human immunodeficiency virus (HIV) coinfection [2]. There has been increasing incidence of TB infection among foreigners who come to Singapore to work or study [3]. Multidrug resistant TB, although low among Singapore-born patients, has been found to be 10 times higher among foreign-born patients, with local transmission in a correctional facility recently reported [4].

The treatment of TB involves combinations of anti-TB drugs including isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA) as there are no better alternatives to these first line agents. However, allergic drug hypersensitivity to TB drugs is not uncommon [5, 6]. Limitations in the use of *in vitro* and *in vivo* diagnostic tests in diagnosing the putative drug in TB drug allergy often necessitates the use of tailored desensitization-rechallenge

(D-R) regimes to reintroduce appropriate TB treatment.

The objective of our study was to describe the results of tailored sequential D-R for anti-TB drug allergy.

MATERIALS AND METHODS

Consecutive patients who had undergone tailored D-R to anti-TB drugs between 1 September 1997 and 31 January 2012 in our centre were analyzed. Following resolution of the acute reaction, anti-TB drug was restarted at as low as 1:6,000 to 1:3 of the final daily dose (FDD) depending on the severity of the initial (index) reaction, with gradual dose escalation daily to the FDD. "Mild" cases were defined as nonbullous, skin limited involvement; "severe" cases were defined as immunobullous/severe cutaneous adverse reactions, drug hypersensitivity syndrome or any other major organ involvement. Single-step daily increments where the index reaction was mild (Table 1), and four-step dose escalations in a day were used where the index reaction was severe (Table 2). Subsequent drugs were sequentially added ≥ 3 days later when the preceding drug was tolerated. The full blood count and liver

Table 1. Example of isoniazid or rifampicin desensitization protocol (multistep daily dose escalation)

Date	Time	Amount to take	Dose of isoniazid or rifampicin slurry/syrup	Cumulative daily dose	Lab tests prior to dose
Day 1, 6-hour dosing	06:00	1 mL of 0.1 mg/mL	0.1 mg	0.1 mg	FBC, Cr, ALT, AST, UFEME
	12:00	5 mL of 0.1 mg/mL	0.5 mg	0.6 mg	
Day 2, 6-hour dosing	06:00	4 mL of 1 mg/mL	4 mg	4 mg	
	12:00	8 mL of 1 mg/mL	8 mg	12 mg	
Day 3, 6-hour dosing	06:00	5 mL of 10 mg/mL	50 mg	50 mg	FBC, ALT, AST
	12:00	5 mL of 10 mg/mL	50 mg	100 mg	
	18:00	5 mL of 10 mg/mL	50 mg	150 mg	
Day 4, BD dosing	08:00	150 mg	150 mg	150 mg	
	20:00	150 mg	150 mg	300 mg	
Day 5, BD dosing	06:00	150 mg	150 mg	150 mg	
	18:00	150 mg	150 mg	300 mg	
Day 6*, OD dosing	06:00	300 mg	300 mg	300 mg	FBC, ALT, AST
Day 7*, OD dosing	06:00	300 mg	300 mg	300 mg	

FBC, full blood count; Cr, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UFEME, urine formed elements and microscopic examination; BD, twice daily; OD, once daily.

*Regime for day 6 can be modified accordingly if rifampicin dose required is 450 mg or 600 mg/day.

function tests were monitored every third day (where the index reaction was severe) or where clinically indicated, and prior to addition of each new drug for early detection of leukocytosis, eosinophilia or elevations in liver enzymes which may suggest recurrence of drug hypersensitivity. The sequence of drugs to add was determined by the attending allergist in consultation with the physician managing the TB infection. Considerations included type of TB infection (first episode or relapse), severity of the initial reaction and end-organ involvement (e.g., hepatitis), concomitant comorbidities, and ability to adhere to non-RIF based regimes (where longer duration of treatment would be needed). All D-R were done as outpatients and included RIF or INH unless the risk of a severe cutaneous reaction (severe Stevens Johnson syndrome [SJS]/toxic epidermal necrolysis [TEN]), drug hypersensitivity syndrome or major organ involvement developing precluded RIF/INH D-R. Patients had access to the Clinical Immunology/Allergy Nurse Clinician at any time should any adverse reaction occur during the procedure. They were reviewed by the allergist every third day, prior to addition of the next drug or when any suspected adverse reaction occurred. This study was approved by the National Healthcare Group Domain Specific Review Board.

RESULTS

There were 11 patients included in the study, of whom 10 were male and 1 female. Eight patients were Chinese, 2 Malay and 1 Indian. TB disease was pulmonary in 6 patients; extrapulmonary in 2 patients who had TB lymphadenopathy and meningitis respectively; and both pulmonary and extrapulmonary in 3 patients, 2 of whom had HIV infection. A summary table of all 11 cases and 25 tailored D-R, with the demographic characteristics, anti-TB drug exposure history, initial reaction, D-R timing/sequence and outcomes is provided in Table 3.

All patients developed nonimmediate reactions during the index (initial) reaction. The mean time to the onset of the index reaction was 30 ± 30 days. All patients developed cutaneous eruptions, where maculopapular exanthema (MPE) was the most common (8 patients). Drug-induced hypersensitivity syndrome (DIHS) occurred in 54.5% (6 patients) of whom all had fever, 83.3% hepatitis, and 83.3% eosinophilia. Two patients developed SJS. The drug regimens causing TB drug allergy comprised RIF, EMB, INH, PZA, and streptomycin (STREP) as follows:

- REHZ (5 patients)
- REH (4 patients)
- RHZ (1 patient)
- REHS (1 patient).

Table 2. Example of isoniazid and rifampicin sequential desensitization rechallenge protocol (single step daily dose escalation)

Day	Drug #1	Dose	Drug #2	Dose	Drug #3	Dose	Lab tests prior to dose
1	Rifampicin	150 mg					FBC, Cr, ALT, AST, UFEME
2	Rifampicin	150 mg					
3	Rifampicin	300 mg					
4	Rifampicin	600 mg					
5	Rifampicin	600 mg	Isoniazid	100 mg			FBC, ALT, AST
6	Rifampicin	600 mg	Isoniazid	100 mg			
7	Rifampicin	600 mg	Isoniazid	200 mg			
8	Rifampicin	600 mg	Isoniazid	300 mg			
9	Rifampicin	600 mg	Isoniazid	300 mg	Pyrazinamide	100 mg	FBC, ALT, AST
10	Rifampicin	600 mg	Isoniazid	300 mg	Pyrazinamide	100 mg	
11	Rifampicin	600 mg	Isoniazid	300 mg	Pyrazinamide	250 mg	
12	Rifampicin	600 mg	Isoniazid	300 mg	Pyrazinamide	500 mg	
13	Rifampicin	600 mg	Isoniazid	300 mg	Pyrazinamide	750 mg	FBC, ALT, AST
14	Rifampicin	600 mg	Isoniazid	300 mg	Pyrazinamide	1,000 mg	

FBC, full blood count; Cr, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UFEME, urine formed elements and microscopic examination.

Ethambutol 100 mg and 400 mg per tablet; Isoniazid 100 mg per tablet; Rifampicin 300 mg per tablet, Streptomycin 1 g per vial.

Table 3. Patient characteristics, initial reaction and outcomes of desensitization-rechallenge

Patient no.	Age (yr)	Sex	Race	Initial reaction	Date of reaction	Time to onset	Drugs implicated	Type of TB	Date of restarted	1st D-R	2nd D-R	3rd D-R	4th D-R	Outcome D-R
1	74	Male	Chinese	MPE, fever, eosinophilia, hepatitis	9 Jun. 1997	12 Days	RHZ	P	1 Sep. 1997	INH	-	-	-	Successful (INH)
2	38	Male	Chinese	MPE	6 Aug. 1998	Un-known	REH	P + EP (LN), (HIV)	7 Sep. 1998	INH	RIF	EMB	-	Failed INH, MPE day 8 Successful (RIF, EMB)
3	34	Male	Chinese	MPE, fever, hepatitis; SJS during physician D-R*	14 Sep. 2005	5 Days	SREH	P	14 Sep. 2005 1 Mar. 2006	STREP*	EMB*	LEV [†]	-	Day 27 SJS* Successful (RIF)
4	32	Female	Chinese	Erythema, urticaria	28 Sep. 2006	9 Days	RHZ	P	6 Nov. 2006 24 Nov. 2006	INH*	EMB*	RIF*	-	Successful (RIF)
5	47	Male	Chinese	MPE, fever, eosinophilia/SJS	28 Dec. 2007	57 Days	REH	P + EP (LN), HIV	21 Jan. 2008	INH	LEV [†]	STREP	-	Successful (INH)
6	65	Male	Chinese	MPE	13 Feb. 2008	12 Days	REHZ	P + EP (meningitis)	24 Feb. 2008	RIF	INH	-	-	Successful (RIF/INH)
7	50	Male	Malay	Erythema, fever, eosinophilia, thrombocytopenia hepatitis	3 Mar. 2010	Unclear	REHZ	P	26 Mar. 2010	EMB*	PZA*	-	-	Failed INH fever, MPE day 3 Successful (INH, EMB, PZA)
8	30	Male	Malay	MPE, hepatitis, eosinophilia	10 Jun. 2010	11 Days	REHZ	EP (LN)	29 Jun. 2011	EMB	PZA	RIF	INH	Successful (RIF, EMB, INH, PZA)
9	23	Male	Indian	MPE	8 Oct. 2010	14 Days	REHZ	EP (meningitis)	13 Oct. 2010	INH	RIF	PZA	-	Successful (RIF, INH, PZA)
10	47	Male	Chinese	Rash, renal, leukopenia, thrombocytopenia	6 Nov. 2010	72 Days	REH	P	1 Nov. 2010	PZA*	LEV*	-	-	PZA hepatitis* LEV anaphylaxis* Successful (RIF, INH)
11	62	Male	Chinese	MPE, fever, hepatitis, leukocytosis, eosinophilia	15 Jul. 2011	80 Days	REH	P	22 Aug. 2011	INH	LEV [†]	STREP	-	Successful (INH)

TB, tuberculosis; D-R, desensitization-rechallenge; MPE, maculopapular exanthema; P, pulmonary; INH, isoniazid; EP, extrapulmonary; LN, lymphadenopathy; HIV, human immunodeficiency virus; RIF, rifampicin; EMB, ethambutol; SJS, Stevens Johnson syndrome; STREP, streptomycin; LEV, levofloxacin; PZA, pyrazinamide.
*D-R carried out by referring infectious disease physician/pulmonologist before referral to allergist. [†]LEV added not considered D-R as no prior exposure.

The D-R regime included at least RIF or INH where possible. D-R was successful in the majority of patients. INH D-R was successful in 7/9 patients (77.8%) starting at 100 mg/day and achieving 300 mg/day within a mean of 4.3 ± 2.3 days. RIF D-R was successful in 7/7 (100%) starting at 3.6–150 mg/day and achieving 450–600 mg/day in 4.4 ± 1.7 days. EMB was successfully used in 3/3 patients (100%) starting at 100–200 mg/day and achieving 800–1,200 mg/day in 5.0 ± 1.0 days. PZA was successfully used in 2/2 patients (100%) starting at 5–100 mg/day and achieving 1,000–1,250 mg/day in 7 days. STREP D-R was successful in 1/1 patient (100%) starting at 100 mg/day and achieving 700 mg/day in 5 days.

There were 2 patients who failed INH D-R: one (patient no. 7) developed fever and MPE on day 3, the other (patient no. 2) developed MPE on day 8. Among patients where the index reaction was DIHS or SJS/TEN, 1 patient (patient no. 3) with DIHS failed D-R with INH when he developed fever and MPE on day 3. Where the initial reaction was SJS, D-R with INH (patient no. 5) and RIF (patient no. 3) respectively was successful in 2 patients.

Overall, there were 23/25 (92%) successful tailored D-R among the 11 patients. All patients completed TB treatment of ≥ 5 months' duration with no cases of drug-resistant TB.

DISCUSSION

Nonimmediate reactions (onset beyond 1 hour) are much more common than immediate reactions to anti-TB drugs. These include MPE, lichenoid drug eruptions [7], haematological reactions, hepatitis, DIHS, SJS and TEN [8]. Genetic polymorphisms in TB drug metabolizing enzymes associated with MPE [9, 10], and HLA-Cw*0401 [11] associated with DIHS have been reported. Multiple concurrent TB drug allergy/hypersensitivity makes it difficult to ascertain the culprit drug from history alone [12]. Lymphocyte transformation tests (LTT) which are often carried out only in highly specialized research laboratories, are not consistently useful as they are often drug-specific and reaction-specific [13–17]. Patch test positivity is also dependent on the type of cutaneous drug eruption and putative drug [18, 19]. Positive patch tests have been reported for INH and EMB associated MPE [20] and eczematous eruptions [21]. Delaying LTT and patch testing to at least 4–6 weeks following the acute reaction in order to accurately identify the causative drug, may not be practically feasible especially where TB infection needs to be urgently treated. Using drug provocation tests (DPT) [22] to identify the culprit drug poses the

problems of how to determine which drug to be challenged first, and increased risk of TB drug resistance when challenging one drug at a time separated by periods of up to 1 week. The process of reintroducing TB drugs sequentially over hours or days likely induces tolerance over time through immunoglobulin G (IgE)-mediated desensitization for immediate reactions [23]. However, the mechanisms of tolerance induction in nonimmediate reactions remain unknown, and the evidence base is less well-established, even though guidelines have been published [24].

There are several key considerations in designing a tailored D-R protocol for TB drug allergy. The target FDD for each anti-TB drug needs to be tailored according to body weight. Comorbid conditions often necessitate target dose adjustments e.g., EMB in renal impairment; INH and RIF in liver disease. Comorbid conditions may also increase the risk of drug interactions e.g., HIV infection and drug interactions with concomitant antiretroviral therapy. The duration of treatment is also determined by the site(s) of infection e.g., bone and joint (6–9 months), central nervous system/meningitis (9–12 months); and whether treatment is for relapsed TB, or drug-resistant TB. Of note, directly observed therapy is advantageous [25] because adverse reactions during D-R can be readily and objectively diagnosed, and adherence during D-R is ensured.

Successful rapid oral desensitization regimes [26] have been described for INH [26–32], RIF [26–29, 33–35], EMB [28, 29], and PZA [29, 36]. The initial (index) reaction in all cases usually involve combinations of REHZ, with the reactions ranging from cutaneous drug eruptions alone to organ-specific/systemic manifestations. Diagnostic tests that have been described in these studies to identify the culprit drug included:

- skin prick test (SPT) for INH [28, 29, 36], RIF [28, 29, 33, 35, 36], EMB [36], PZA [36]
- SPT and intradermal tests for INH and RIF [27–29]
- cellular allergen stimulation tests for RIF-specific IgE [35]
- LTT for INH [17, 30, 31], RIF [17, 30, 34], EMB [17], PZA [17, 30]
- DPT for INH [30–32].

Unfortunately, the sensitivity, specificity, and predictive values of these tests are variable depending on the type of initial acute reaction; and are not universally available in every country. The 11 patients had not been on any other new medications in the 1 month prior to the initiation of the TB drugs. In the absence of well-validated *in vivo* and *in vitro* tests for TB drug allergy (including Elispot tests, LTT and patch tests), it becomes clinically impossible to determine which of the TB drugs alone/in combination resulted

in the reaction. In particular, based on epidemiological patterns of TB drug allergy, INH and RIF are usually the putative drugs and it is usually impossible to differentiate either of them.

More than one anti-TB drug often needs to be reintroduced, with a 3- to 5-day interval before addition of a new drug, because leaving patients on anti-TB drug monotherapy would increase the risk of emergence of drug-resistant TB. The risks versus benefits of desensitization need to be explained carefully to the patient where combinations of second-line anti-TB drugs (e.g., quinolones, dapsone, cycloserine) are deemed not preferable, especially in regions with increasing incidence of drug-resistant TB for which second-line agents are usually reserved [37].

Although organ-specific hypersensitivity should preclude the use of DPT to identify the putative drug, DPT has been used in the diagnosis of INH induced pneumonitis [30] and hepatitis [31, 32], where subsequent desensitization were successful. In cases where the index reaction was SJS where D-R is generally contraindicated, D-R to any of the TB drugs has been shown to be successful in the majority of cases, including in HIV-infected individuals [38]. The index SJS reaction was mild oral and genital ulcers with no ocular involvement. Neither of the SJS patients developed SJS during D-R. Patient no. 3 (Table 3) had developed SJS to STREP/levofloxacin (LEV)/EMB following D-R by his attending pulmonologist on day 27. The initial reaction involved SREH; as such RIF/INH were deemed unlikely. Thus the RIF D-R was done as an outpatient, with success. Patient no. 5 developed SJS to REH in the index reaction, which comprised mild oral and genital ulcers with no ocular involvement. Thus he received INH D-R INH followed by LEV/STREP which he had not received before, again successfully.

The decision points on which drug to initiate D-R were based on several factors, in the absence of availability of well-validated *in vitro* and *in vivo* tests to identify the culprit anti-TB drug:

- Prior attempt at D-R by referring physician: in 4 of the cases (3, 4, 7, 10), the referring infectious disease physician/pulmonologist had initiated their own D-R which failed, hence the patients were subsequently referred to an allergist. Among our hospitals, it was not uncommon for infectious disease physicians/pulmonologists to initiate their own D-R. In the majority of cases, they were successful especially where the initial reaction was a mild rash;
- Change in practice from initiating the less allergenic drugs to RIF-based regimens: as the study cases spanned over 10 years, in the late 1990s/early 2000s, the initial practice/philosophy among infectious diseases (ID) physicians/pulmonologists

treating TB was to restart treatment with the less likely drug. This was usually EMB/PZA (the latter provided the initial reaction did not result in hepatitis). If there was no adverse reaction, INH, RIF or alternative drugs like STREP or LEV was then added sequentially. In the latter 2000s, RIF became the “cornerstone” drug of TB therapy in view of INH resistance, and the longer regimens needed for second line or non-RIF based therapies;

- Variation in preferred TB-drug regime among different ID physicians/pulmonologists;
- Heterogeneity in the clinical presentations of the patients.

There remains little agreement worldwide whether the initial drug should be the most effective drug (RIF/INH), or instead the one with the least likelihood of being the cause of the initial reaction. The argument is that even though INH and RIF are generally associated with higher risks of reactions upon reintroduction [39, 40], tolerance to these 2 highly effective drugs shortens the overall duration of TB treatment. Desensitization and DPT are usually contraindicated in DIHS and SJS. Thus it should only be carried out very cautiously, where no better alternative therapies are available, after a careful risk-benefit assessment in discussion with the patient and with informed consent from the patient. Where the initial reaction was SJS, D-R with INH and RIF respectively was also successful in 2 patients in our cohort, as has been reported elsewhere [38]. However, these results have to be interpreted with extreme caution.

The tailored D-R were performed in the outpatient clinic, with close monitoring over 8 hours. Where necessary, patients returned for review daily or on alternate days. The patients were given mobile phone access to the nurse clinician should they run into problems or develop a reaction upon discharge. As Singapore is a small island, the patients are able to access the hospital’s Emergency Department very quickly within 30–60 minutes.

As all the patients in our cohort developed nonimmediate reactions, the time intervals between dose escalations (doubling) were 24 hours apart rather than within 15–60 minutes which are the time intervals usually used in rapid desensitization for immediate reactions [27–29, 36]. FDD was achieved within 8–12 hours or by the second day. Regimens for SJS have included a 24-hour break between dose escalations, addition of a second anti-TB drug one week later, and achieving optimal dosing of a 4-drug combination in 4 weeks [38]. These have been shown to be safe with successful completion of TB treatment without morbidity and mortality. Regimens with much slower dose escalations, 12-steps,

and premedication with prednisolone and hydroxyzine have been reported for the treatment of atypical Mycobacterial infections where patients failed initial desensitization to EMB [41].

In conclusion, tailored sequential TB drug D-R is successful with careful dose escalation and close monitoring. In DIHS and SJS, D-R is contraindicated. It should only be carried out very cautiously, where no better alternative therapies are available, after a careful risk-benefit assessment in discussion with the patient and with informed consent. Close monitoring with periodic laboratory tests including full blood count, renal and liver function tests, can prevent severe adverse reactions.

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