

## Case Report

# Safety of oral graded challenges as a diagnostic approach hypersensitivity reaction to anti-tuberculosis drugs: a case report

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## ABSTRACT

Tuberculosis (TB) still becomes a significant health problem in developing countries, especially in Indonesia. Allergy to antitubercular drugs is a real hindrance to the management of TB. The first-line anti-TB drug (ATD) is still the most effective TB drug, but it can have some side effects. One of these side effects is drug hypersensitivity reactions (DHR) which can affect a patient's compliance. The recommended diagnostic approach to DHR is a graded challenge by introducing drugs safely and optimally under a threshold dose until the usual daily dose is reached. We present a case of DHR to ATB drug and oral graded challenge as the diagnosis approach.

**Keywords:** Graded challenges, Safety, DHR

## INTRODUCTION

TB is an infectious disease that is primarily caused by a rod-shaped bacteria called *Mycobacterium tuberculosis*. Besides *M. tuberculosis*, several bacteria cause TB infection such as *M. africanum*, *M. microti*, and *M. Bovis*.<sup>1</sup> *Mycobacterium tuberculosis* can spread from one part of the body to another through the blood or lymphatic pathways. Based on the site infected, TB can be categorized into two: pulmonary TB and extra pulmonary TB.<sup>1</sup> An estimated 9.9 million people suffer from TB worldwide in 2020. In Indonesia, the number of cases treated and found in the period 2021-2022 was around 701,590 cases with an 86 % treatment success rate using Anti TB Drug regimen.<sup>2,3</sup> TB treatment must be carried out as soon as confirmed before it progresses to worsening. The important use of ATD must be accompanied by monitoring the side effects and must be remembered that consuming multidrug regimens could lead to severe side effects associated with ATD and increased risk of DHRs. DHR is an unpredictable reaction and it refers to an immunologically mediated hypersensitivity reaction.

Unconfirmed drugs allergy poses substantial public health consequences.<sup>4</sup> A Graded Oral Challenge is a valuable tool for diagnosing specific allergies or the absence of them, allowing the physician to further modify the treatment. We present a case of DHR related to ATD, and the oral graded challenges as a diagnostic tool for DHRs.

## CASE REPORT

A 26-year-old female patient presented to Wangaya hospital to start ATD treatment after she was confirmed with TB lymphadenitis. The patient presented overall optimal condition with stable hemodynamics. She had a history of drug allergy during the anamnesis, but the offending drug was unclear. In order to prevent DHR in patients with an unclear history of allergy to ATD regimen consisting of 400 mg isoniazid, 450 mg rifampicin, 750 mg ethambutol, and 1000 mg pyrazinamide, we decided to perform oral graded challenges for each component of ATD to determine if there is any offending drug or a threshold dose that can cause DHR. The patient returned to the hospital to start oral graded challenges of ATD, After the first graded challenge is done, the next graded

challenge will be continued with an interval of 7 days for clearance, and also the patient must be clinically stable. The patient signed an informed consent form and was admitted to 1 daycare to observe if there is any chance of DHRs. There was no DHR related to isoniazid, ethambutol, and rifampicin but there was DHR related to pyrazinamide (Table 4). DHR occurred at step III of the oral graded challenge, cumulative time 60 min, drug concentration 3/10, with cumulative dose 600 mg. DHR

was considered positive because there were some symptoms or signs of an immediate drug reaction as urticaria, skin rashes, and pruritus at about 30 min after the last dose was administered. We established the diagnosis of DHRs to ATD (pyrazinamide). The patient was treated with intravenous dexamethasone and diphenhydramine and added Methylprednisolone with cetirizine by oral upon discharge. The patient was discharged from the hospital in stable and good condition.

**Table 1: Graded challenges of ATD isoniazid 400 mg.**

Steps	Time (min)	Cumulative time (min)	Drug concentration (mg)	Dose (mg)	Cumulative dose (mg)	DHR
<b>I</b>	0	0	1/10	40	40	None
<b>II</b>	30	30	2/10	80	120	None
<b>III</b>	30	60	3/10	120	240	None
<b>IV</b>	30	90	4/10	160	400	None

**Table 2: Graded challenges of ATD ethambutol 750 mg.**

Steps	Time (min)	Cumulative time (min)	Drug concentration (mg)	Dose (mg)	Cumulative dose (mg)	DHR
<b>I</b>	0	0	1/10	75	75	None
<b>II</b>	30	30	2/10	150	225	None
<b>III</b>	30	60	3/10	225	450	None
<b>IV</b>	30	90	4/10	300	750	None

**Table 3: Graded challenges of ATD rifampicin 450 mg.**

Steps	Time (min)	Cumulative time (min)	Drug concentration (mg)	Dose (mg)	Cumulative dose (mg)	DHR
<b>I</b>	0	0	1/10	45	45	None
<b>II</b>	30	30	2/10	90	135	None
<b>III</b>	30	60	3/10	135	270	None
<b>IV</b>	30	90	4/10	180	450	None

**Table 4: Graded challenges of ATD pyrazinamide 1000 mg.**

Steps	Time (min)	Cumulative time (min)	Drug concentration (mg)	Dose (mg)	Cumulative dose (mg)	DHR
<b>I</b>	0	0	1/10	100	100	None
<b>II</b>	30	30	2/10	200	300	None
<b>III</b>	30	60	3/10	300	600	(+) mild DHR
<b>IV</b>	Not administered					

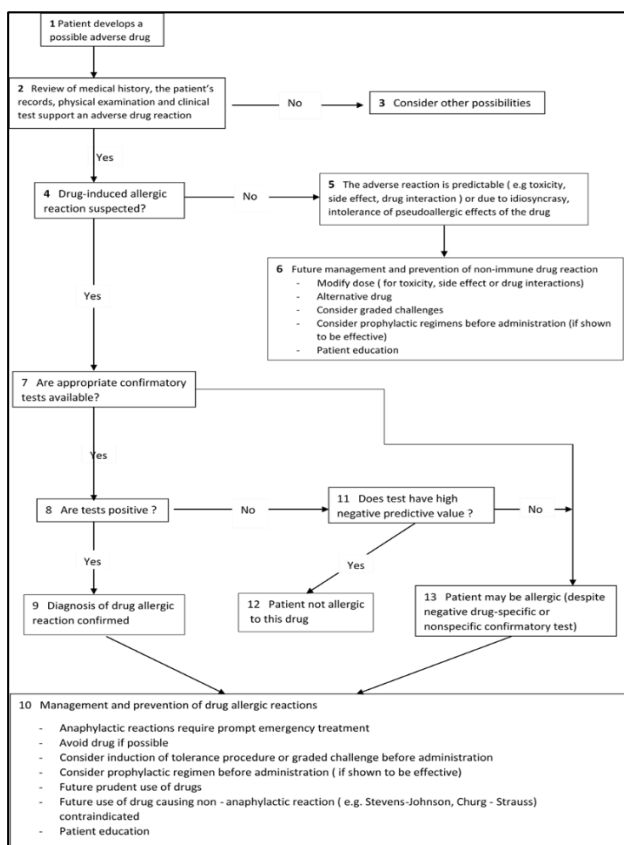
## DISCUSSION

DHRs result in major health problems and could lead to severe complications. Some known clinical manifestations of hypersensitivity reactions due to ATD drugs such as urticaria, generalized pruritus, maculopapular exanthema, lichenoid eruptions, fixed drug eruption, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.<sup>9,10</sup> DHRs are broadly categorized into predictable (type A) and unpredictable (type B) reactions. Predictable reactions are usually dose-dependent, are related to the known pharmacologic actions of the drug, and occur in otherwise healthy individuals.

Unpredictable reactions are generally dose-independent, are unrelated to the pharmacologic actions of the drug, and occur only in susceptible individuals. Unpredictable reactions are subdivided into drug intolerance, drug idiosyncrasy, drug allergy, and pseudo-allergic reactions. Both type A and type B reactions may be influenced by the genetic predisposition of the patient.<sup>6</sup> Two strategies that can be implemented in patients with a reported allergy are graded dose challenge (GDC) and desensitization (DSENS).<sup>7</sup> Graded dose challenge assesses a patient's ability to tolerate a therapy or a related one, while desensitization provides the ability to administer a drug (or related drug) despite a convincing IgE-mediated allergy.<sup>6</sup>

There are 4 known types of drug tolerance mechanisms: IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms. All procedures to induce drug tolerance involve administration of incremental doses of the drug. Through various mechanisms, these procedures induce a temporary state of tolerance to the drug, which is maintained only as long as the patient continues to take the specific drug.<sup>6</sup>

Oral graded challenge is a cautious administration of a medication to a hospitalized patient with a low-to-moderate risk for a true IgE-mediated reaction. The main purpose of the graded challenge is to administer the drug with caution to patients who are unlikely to be allergic to the drug. Patients who tolerate graded challenges are considered to not be allergic to the drug and do not have an increased risk of future reactions compared to the general population. A graded challenge typically involves 2 or 4 steps, increasing doses are administered every 30 to 60 minutes until the full therapeutic dose is reached.<sup>8</sup> This procedure has also been approved by the joint task force on practice parameters, representing the American academy of allergy asthma and immunology; the American college of allergy, asthma and immunology; and the joint council of allergy, asthma and immunology.



**Figure 1: Algorithm for disease management of drug allergy.<sup>6</sup>**

The choice of whether to introduce a clinically indicated drug via graded challenge or via induction of drug

tolerance is mainly based on their history and/or diagnostic test results, patients who are unlikely to be allergic to a drug may undergo graded challenge. Patients who have a relatively higher likelihood of being allergic to a drug should undergo an induction of drug tolerance procedure.<sup>6</sup> Graded challenge (or induction of drug tolerance) should almost never be performed if the reaction history is consistent with a severe non-IgE-mediated reaction, such as SJS, TEN, interstitial nephritis, hepatitis, or hemolytic anemia.<sup>6</sup>

In this case, we confirmed that the patient has DHR to ATD (pyrazinamide), we choose graded challenge as a diagnostic approach because the history of drug allergy was unclear and the patient was unlikely to develop any DHR to ATD. Corticosteroids and anti-histamine have been given to reduce DHR symptoms. We suggest that patient should avoid the offending drug (pyrazinamide) or administer via desensitization.

## CONCLUSION

DHR is an unpredictable reaction. The use of multidrug regimens has been associated with an increased risk of DHR and should be administered with caution. Patients, who develop symptoms consistent with an IgE-mediated reaction during the graded challenge, should not receive further offending drug or administer via desensitization. The safety of drug challenge needs to be further addressed with a retrospective review of larger databases, a prospective study in a truly allergic population, or a survey study similar to those assessing the safety of immunotherapy.

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