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Case Report

Drug-Induced Hypersensitivity Reaction and Re-Introduction of Anti-Tubercular Drugs (ATT): A Case Report and Review of Literature

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Abstract

Tuberculosis (TB) is a communicable disease caused by the bacillus *Mycobacterium tuberculosis* and is the leading cause of death by a single infectious agent overall. According to the WHO Global TB Report, India contributes to 26% of the global burden of TB. Currently, a four-drug regimen comprising Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol is approved for the treatment of drug-sensitive TB. The management of cutaneous adverse drug reactions to anti-tubercular drugs is akin to a double-edged sword, with discontinuation of ATT increasing the risk of developing disseminated and drug-resistant tuberculosis, and continuation leading to persistence or exacerbation of the adverse drug reaction (ADR). The risk of developing an ADR to anti-tubercular therapy (ATT) varies from 8 to 85% in various studies [10]. The prevalence of rashes associated with ATT shows that the maculopapular rash (42.5%) is the most frequently observed type, followed by urticarial, lichenoid, DRESS, AGEP, and exfoliative dermatitis (17). The drugs associated with Cutaneous ADRs from the lowest to the highest risk are Isoniazid, Rifampicin, Pyrazinamide, Ethionamide, Cycloserine, Ethambutol, Para-aminosalicylic acid (PAS), and Streptomycin (25). We present a case and approach to the re-introduction of first-line anti-tubercular drugs after hypersensitivity with fixed-dose combinations.

Keywords: Tuberculosis, *Mycobacterium tuberculosis,* adverse drug reaction, anti-tubercular therapy

Case Presentation:

61-year-old male, a chronic smoker for 30 years, known case of type 2 diabetes mellitus hypothyroidism and hypertension presented with a history of hoarseness of voice for 1.5 months. He had a history of fever with night sweats, loss of appetite, loss of weight, and cough. On evaluation, a single pulmonary nodule was detected on a contrast-enhanced CT scan of the chest in the right upper lobe. A biopsy of the nodule showed necrotizing granulomas and a provisional diagnosis of tuberculosis was made based on the histopathologic findings. He was started on a first-line fixed-dose combination of anti-tubercular drugs.

10 days after introducing fixed-dose dose ATT, the patient developed itching, swelling, and burning sensation all over the body, which was relieved with anti-histamines. ATT was stopped and reintroduced after 1 week following which he had a similar episode associated with shortness of breath and chest tightness which was managed as an anaphylactic reaction. He was thereafter referred to our institution.

The patient was admitted for the reintroduction of ATT. Fixed dose ATT was stopped and was started on modified ATT-Levofloxacin, Linezolid, and Ethambutol.

First-line ATT was introduced sequentially, starting from the drug with the lowest potential for hypersensitivity reaction, at the lowest dose, and gradually escalating to the appropriate dose with continuous monitoring of symptoms and vitals.

Isoniazid was introduced at a dose of 50mg and symptoms were observed. The dose was gradually escalated to the appropriate dose of 300 mg without any hypersensitivity reaction. Linezolid was discontinued on the reintroduction of Isoniazid at the appropriate dose. This was followed by the reintroduction of Pyrazinamide at a dose of 250 mg which was gradually escalated to 1500 mg without any adverse reaction. Symptoms and vitals were regularly monitored and were stable. Rifampicin was introduced at a dose of 50 mg following which the patient developed a hypersensitivity reaction in the form of rash in upper and lower limbs, itching, and shortness of breath. It was managed as an anaphylactic reaction with anti-histamines and oxygen support, following which the symptoms resolved. Hypersensitivity reaction was thereby attributed to Rifampicin and the patient was discharged on Isoniazid, Levofloxacin, Pyrazinamide, and Ethambutol and followed up.

Outcome and follow-up:

The patient was followed up telephonically and is currently doing well with improvement in appetite and weight gain

Discussion:

According to the World Health Organization (WHO), a Drug Hypersensitivity Reaction (DHR) is classified as a significant adverse drug reaction (ADR) characterized by "objectively reproducible symptoms or signs that arise following exposure to a specific stimulus at a dose that is typically well-tolerated by individuals without hypersensitivity". A drug reaction with demonstrated immunological mechanisms, either antibody or cell-mediated, is referred to as a drug allergy [1]. DHRs can be classified as immediate or nonimmediate DHRs depending on the onset time after drug exposure. Immediate Drug Hypersensitivity Reactions (DHRs) generally manifest within 1-6 hours following drug exposure, while non-immediate DHRs can occur at any time after 1 hour of drug administration [2]. The severity of clinical presentations associated with DHRs can range from mild, such as urticaria, to severe conditions like Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome or Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) [3, 4].

Table 1: Comparison of various studies done on Anti-tubercular therapy-induced cutaneous hypersensitivity [17]

	Thong et al (2014)	Tan WC et al (2007)	Lehloenya et al (2011)
Maculopapular	8 (72%)	34 (72.3%)	2
Urticarial	1	4 (8.5%)	-
Erythema multiforme	-		-
Steven Johnson Syndrome/ Toxic epidermal necrolysis	-	-	13/17 (20/26%)
Drug Reaction Eosinophilia and Systemic Symptoms	2	-	25 (38%)
Erythroderma	-	1	-
Lichenoid Rash	-	1	3
Other	-	1 (generalized pruritus)	5 (SJS-TEN)
Total	11	47	65

Adverse Drug Reactions (ADRs), including Drug Hypersensitivity Reactions (DHRs) to highly effective first-line anti-TB drugs, carry significance due to their potential to restrict the use of these medications and lead to increased loss to follow-up, treatment failure, and relapse [5-8]. Additionally, when DHRs to multiple drugs arise [9], treating tuberculosis becomes challenging due to the limited availability of effective and well-tolerated anti-TB drugs.

In a study by Shin et al [10], Anti TB drugs were discontinued in patients with suspected DHR based on the decision of the attending physician. Following this, a combination of second-line anti-TB drugs was initiated or anti-TB drugs were withdrawn during drug challenge tests. Characteristics of multiple (a hypersensitivity reaction to two or more chemically distinct drugs) and single DHRs (a hypersensitivity reaction to a single drug) associated with anti-TB drugs were compared. In both the single and multiple Drug Hypersensitivity Reaction (DHR) groups, Rifampin emerged as the primary culprit. The discontinuation of effective anti-TB drugs, including Rifampin, as a result of DHRs, played a significant role in the reduced treatment success rate observed in this study.

Earlier research has established a correlation between genetic variations of the CYP2C19 and CYP2C9 genes and the development of skin rash induced by first-line anti-tuberculosis drugs [11,12]. A recent study conducted in Korea further revealed that tuberculosis patients possessing specific ABCC2 gene haplotypes or polymorphisms were at a heightened risk of experiencing skin rash following the administration of first-line anti-tuberculosis medications [13].

The reported incidence of cutaneous adverse drug reactions (ADRs) in patients undergoing antitubercular therapy is 5.7%. [14]. It ranks third amongst adverse effects associated with ATT after impaired liver function and gastrointestinal disorders. All first-line ATDs can cause rashes. The incidence of first-line ATD CADR is 2.38% in pyrazinamide; 1.45% in streptomycin; 1.44% in ethambutol; 1.23% in rifampicin; and 0.98% in isoniazid [25].

Various risk factors associated are genetic susceptibility, elderly age group, female gender, diabetes, organ failure, polypharmacy, infections such as HIV, EBV, autoimmune diseases (rheumatoid arthritis, Sjogren's disease, SLE), malignancy especially hematological, and fixed-dose combinations of ATT [15-17]. The elderly age group is prone to adverse reactions due to polypharmacy, reduced renal excretion, variable drug absorption, and metabolism by the liver. In old age, there is a decrease in the body's water content, while the proportion of fat increases. Water-soluble drugs thereby reach higher concentrations and fat-soluble drugs accumulate more due to increased fat to store them. CADRs are relatively less common in males due to the potential microsomal-inducing effects of androgens. Additionally, females, in comparison to males, typically have lower body weight, smaller organ size, higher body fat percentage, different gastric motility, and a decreased glomerular filtration rate. These physiological differences can alter the pharmacokinetics and pharmacodynamics of drugs. [18]. Patients with diabetes have an increased susceptibility to adverse drug reactions (ADRs) due to factors such as oxidative stress and polypharmacy [19]. Smoking, on the other hand, impacts the metabolic process by functioning as a liver enzyme inducer, specifically affecting hepatic cytochrome P450 enzymes. [18].

After the introduction of fixed-dose combination (FDC) antituberculosis therapy (ATT) in India in 2016, which involved a switch from intermittent therapy to a daily regimen tailored to the patient's body weight, a slight increase in the

incidence of drug reactions was observed. However, this could be attributed to several factors, such as an enhanced rate of tuberculosis detection, improved adherence to treatment, early detection of cutaneous adverse drug reactions (CADRs), or potentially the increased dosage of drugs administered daily compared to the previous thrice-weekly regimen.

The latency period for the onset of rash following drug intake ranged from 3 days to 150 days, with a mean duration of 33 days [20]. Urticarial rash typically appeared within days to weeks, whereas lichenoid rash manifested after several months of initiating antituberculosis therapy (ATT). However, the majority of patients experienced the development of rash within the initial 2 months of treatment, which occurred prior to completing the intensive phase of ATT. [21].

Table 2: The degree and severity of allergic skin reactions with Anti Tubercular therapy [28]

Severity	Clinical symptoms
1st degree	Moderate Itching or reddish rash
2nd degree	Maculopapular rash ± itching
3rd degree	Papular, vesicular, wet rashes, purpura, skin or mucosal ulcer
4th degree	Bullous lesions (Steven Johnson Syndrome), Febrile erythroderma, Skin necrosis (Toxic Epidermal Necrolysis)

The most common type of rash seen with ATT was maculopapular rash (42.5%) followed in frequency by urticarial, lichenoid, DRESS, AGEP, and exfoliative dermatitis [17]

The drugs which cause allergic reactions from the lowest to the highest risk are Isoniazid, Rifampicin, Pyrazinamide, Ethionamide, Cycloserine, Ethambutol, Para-aminosalicylic acid (PAS), and Streptomycin. The desensitization is based on the order of the drug list.[26] American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) recommends re-challenging ATD can be given 2-3 days after symptoms improve [27].

Discontinuing ATT increases the risk of disseminated disease and drug-resistant tuberculosis. Therefore, re-challenge should be initiated as early as possible considering it is relatively safe. There are no specific re-challenge guidelines, re-challenge can be done with each ATT drug as per the institution's protocol till the culprit drug is found and a final regimen established. [17]

Re-challenge is defined as a controlled administration of a drug to diagnose drug hypersensitivity reactions.[22] Tuberculosis outcomes are better if a re-challenge is undertaken and only the offending drug is removed from the treatment regimen.[23] Re-challenge is of utmost importance because of the increased burden of TB in India/the World, a limited number of first-line ATT drugs, increased toxicity of second-line drugs, and keeping second-line drugs reserved for resistant cases. By preventing treatment interruption caused by adverse drug reactions (ADRs), it significantly reduces morbidity, mortality, and the transmission rate. It is crucial to avoid therapy interruption, particularly during the intensive phase, as studies have shown that such interruptions are associated with a threefold higher risk of death.[21]

The optimal sequence for re-challenging with anti-tuberculosis drugs is still a subject of debate, whether to prioritize re-challenging with the most effective drugs, rifampicin and isoniazid, or with drugs least likely to cause a reaction. However, it is important to note that all first-line drugs have the potential to cause cutaneous adverse drug reactions (CADRs), and there are no comprehensive studies available to quantify the contribution of each individual drug. To minimize the risk of developing drug resistance, it is suggested to re-challenge with rifampicin and isoniazid, as their use in tuberculosis treatment has been associated with superior outcomes [23]. It is noteworthy that more than 90% of re-challenge reactions occur within 72 hours. Hence, a recommended approach is to re-challenge with a new first-line drug every 96 hours while closely monitoring for any signs of a re-challenge reaction [23].

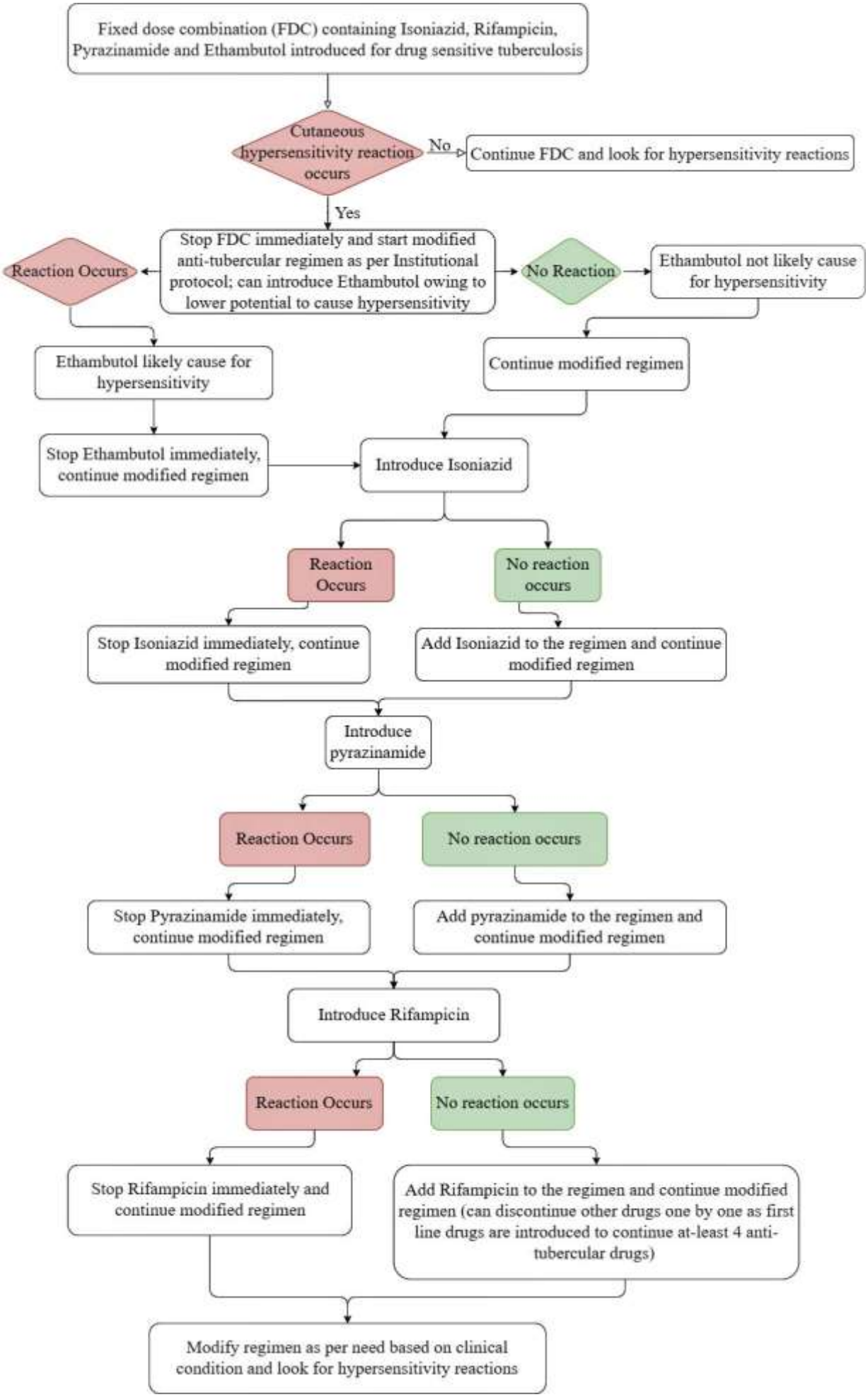
Learning points/Take home points:

While administering fixed dose ATT caution has to be taken to observe for hypersensitivity reactions. Combination therapy has to be stopped and second-line ATT (Fluoroquinolones/ Linezolid) has to be started to bridge the gap of first-line anti-tubercular therapy. Individual drugs must be administered and follow hypersensitivity-causing potential, with continuous monitoring of symptoms and vitals.

The drug with the least potential to cause an adverse reaction is to be started at the lowest dose and gradually escalated each day till the appropriate dose, followed by the next drug with a higher potential than the former. Care has to be taken to observe for any hypersensitivity reaction and the availability of emergency drugs to manage anaphylaxis and anaphylactic shock is to be ensured

General pointers:

1. Goal is to introduce as many first-line anti-tubercular drugs as possible with minimum side effects
2. Each time a new drug is introduced, it has to be done at the lowest dose available for that formulation, which has to be given for 1-2 days with continuous monitoring of vitals and observing any cutaneous hypersensitivity
3. If a hypersensitivity reaction occurs, the newly introduced drug has to be stopped immediately to avoid life-threatening complications and immediate treatment has to be given
4. Always look for hypersensitivity reactions with multiple drugs present in the fixed-dose combination.
5. For effective therapy of tuberculosis we prefer at least 3 drugs in the regimen
6. From least to the highest, the risk for hypersensitivity is Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol


Fixed dose combination (FDC) containing Isoniazid, Rifampicin, Pyrazinamide and Ethambutol introduced for drug sensitive tuberculosis
Cutaneous hypersensitivity reaction occurs
No
Continue FDC and look for hypersensitivity reactions
Yes
Stop FDC immediately and start modified anti-tubercular regimen as per Institutional protocol; can introduce Ethambutol owing to lower potential to cause hypersensitivity
Reaction Occurs
No Reaction
Ethambutol not likely cause for hypersensitivity
Ethambutol likely cause for hypersensitivity
Continue modified regimen
Stop Ethambutol immediately, continue modified regimen
Introduce Isoniazid
Reaction Occurs
No reaction occurs
Stop Isoniazid immediately, continue modified regimen
Add Isoniazid to the regimen and continue modified regimen
Introduce pyrazinamide
Reaction Occurs
No reaction occurs
Stop Pyrazinamide immediately, continue modified regimen
Add pyrazinamide to the regimen and continue modified regimen
Introduce Rifampicin
Reaction Occurs
No reaction occurs
Stop Rifampicin immediately and continue modified regimen
Add Rifampicin to the regimen and continue modified regimen (can discontinue other drugs one by one as first line drugs are introduced to continue at-least 4 anti-tubercular drugs)
Modify regimen as per need based on clinical condition and look for hypersensitivity reactions

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