

DRUG REACTIONS ASSOCIATED WITH ANTITUBERCULOSIS DRUGS

B Kakande | MD

RJ Lehloeny | BSc, MBChB, FCDerm(SA)

Division of Dermatology, Department of Medicine, University of Cape Town

Email | rannakoe.lehloeny@uct.ac.za

ABSTRACT

Tuberculosis continues to be a major cause of death worldwide, mainly driven by the HIV pandemic in Sub-Saharan Africa. Management of tuberculosis-HIV co-infection is fraught with challenges including a higher incidence of adverse drug reactions, complex drug interactions, overlapping toxicities and tuberculosis-associated immune reconstitution inflammatory syndrome. All first-line antituberculosis drugs can cause severe drug reactions. The limited number of effective antituberculosis drugs, compounded by lower efficacy and higher toxicity of second-line drugs, makes treatment of tuberculosis following adverse drug reactions a major challenge. In this review, the clinical spectrum of cutaneous adverse drug reaction to antituberculosis drugs, management of these reactions and challenges clinicians face in continuing tuberculosis treatment will be discussed.

BACKGROUND

Tuberculosis continues to be a major cause of death worldwide. The disease was directly responsible for 1.5 million deaths in 2013. The HIV pandemic has been a strong driver of the high incidence of tuberculosis. Approximately 13% of new cases of tuberculosis worldwide in 2013 were HIV co-infected. This figure climbs above 50% in sub-Saharan countries where there is a high HIV prevalence.¹ Management of HIV tuberculosis co-infection is fraught with management challenges including Adverse Drug Reactions (ADR), complex drug interactions, overlapping toxicities and tuberculosis-associated immune reconstitution inflammatory syndrome. ADR are significantly more common in HIV-infected persons.^{2,3} Both first and second-line antituberculosis drugs are a well-established cause of ADR among those co-infected with tuberculosis and HIV.⁴ The incidence of ADR in HIV has been estimated to be as high as 27% in a primary health care clinic in Cape Town.³

The spectrum of tuberculosis-associated ADR ranges from minor to life-threatening, including delayed-type Cutaneous Adverse Drug Reactions (CADR), immediate-type hypersensitivity reactions, drug induced liver injury, nausea and vomiting, arthralgia, peripheral neuropathy, vertigo, and psychosis.^{4,5} In this review the focus will be on delayed-type CADR to antituberculosis drugs and their clinical presentations and management challenges.

CLINICAL SPECTRUM OF TUBERCULOSIS-ASSOCIATED CADR

The skin responds in a limited manner to a wide spectrum of

insults. As a result, it is often difficult to correctly diagnose CADR. This has clinical implications as different subtypes of CADR carry different prognosis and are managed differently. The clinical spectrum includes Morbilliform (measles-like) Drug Eruption (MDE) commonly referred to as maculopapular eruption, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), Lichenoid Drug Eruption (LDE) and Fixed Drug Eruptions (FDE).

MORBILLIFORM DRUG ERUPTION

Morbilliform Drug Eruption (MDE), also called maculopapular rash, is the most common type of CADR. The rash usually spreads centrifugally with the lesions becoming progressively confluent. MDE are usually self-limiting without systemic involvement (Figure 1).⁶ However, it can be difficult to differentiate MDE from early SJS/TEN and DRESS syndrome.

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, which is also commonly referred to as drug hypersensitivity syndrome, is the most common of the severe forms of CADR. It is characterised by pruritus, pyrexia, fever, oedema, lymphadenopathy, white cell abnormalities (leucocytosis, eosinophilia or atypical lymphocytosis) and hepatitis. The latency period usually exceeds three weeks. Apart from the liver, the other internal organs that may be affected include the lungs, pancreas, kidneys and the heart. The rash in DRESS



Figure 1: Morbilliform or maculopapular rash showing distinct papules in a background of erythema

syndrome has variable morphology, ranging from urticarial, maculopapular, vesicles, pustules, purpura, targetoid lesions, or erythroderma (Figure 2).⁷ Deranged laboratory parameters may lag behind the rash by a few days. The differential diagnosis of DRESS syndrome includes viral exanthemata and inflammatory skin conditions. DRESS syndrome usually responds well to withdrawal of the offending drug and potent topical steroids. In severe cases with marked internal organ involvement, systemic steroids may be warranted. The most common causes of death in DRESS syndrome, estimated at 10%, are liver failure and sepsis.⁷

STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are considered to be a spectrum of the same disease. They are delineated by percentage body surface area of epidermal necrosis and stripping. In SJS, there is less than 10% of epidermal detachment and in TEN, there is greater than 30%. The SJS/TEN overlap lies between these two extremes.⁸ Early SJS/TEN presents with fever, malaise, cough, stinging eyes, a sore throat and palmoplantar tenderness (Figure 3). This constellation of symptoms is often confused with upper respiratory tract infection and treated with antibiotics. These are subsequently blamed incorrectly as the offending drugs. Withdrawal of the offending drug and referral to a centre experienced in managing SJS/TEN improve outcomes.^{9,10} Mortality in TEN, the more severe form of the disease, can be as high as 40%. Most commonly this results from skin and mucosal failure and subsequent bacterial systemic infections.^{11,12} Management of SJS/TEN is controversial. Systemic corticosteroids, immunosuppressive therapy, and intravenous immunoglobulins have not defined their role in the management of SJS/TEN. Supportive therapy by a multidisciplinary team is the mainstay of treatment in most centres. Important aspects of supportive care include:

- Monitoring of vital signs for early detection of systemic infection;



Figure 2: DRESS syndrome showing urticarial papules coalescing to form plaques

- Careful protection of the exposed dermis and early re-epithelialising skin with non-adherent sterile dressings;
- Pain management;
- Fluid balance;
- Temperature control;
- Early referral to ophthalmologists to prevent permanent eye damage;
- Genital care for females and uncircumcised males to prevent adhesions;
- Adequate nutrition, preferably non-abrasive, bland oral feeds at room temperature. Oral intake prevents oesophageal adhesions.¹³

LICHENOID DRUG ERUPTIONS

Lichenoid Drug Eruptions (LDE) present insidiously as pruritic purplish macules and plaques (Figure 4). The interval between drug initiation and a clinically detectable rash varies considerably in LDE. This, together with a lack of detectable acute blood markers, often makes it difficult to establish a temporal relationship with the offending drug and ascribe causality. This creates a major management challenge in setting of polypharmacy and limited number of effective drugs. This is illustrated in the treatment of tuberculosis where all first-line drugs can cause LDE, hindering identification and withdrawal of only the offending drug.

FIXED DRUG ERUPTION

Fixed Drug Eruption (FDE) usually presents as solitary or numerous itchy, round well-circumscribed, erythematous macules or indurated plaques on the skin or mucosal surfaces. The lesions rarely become bullous. FDE tends



Figure 3: Toxic Epidermal Necrolysis showing areas of epidermal necrosis, blisters and stripping

to recur within hours on the same site when re-exposed to the drug, sometimes with new lesions erupting elsewhere (Figure 5). They typically resolve with persistent hyperpigmentation of the involved sites.¹⁴

CHALLENGES IN THE MANAGEMENT OF ANTITUBERCULOSIS DRUG CADR

All the first-line antituberculosis drugs can cause multiple types of CADR, and a specific type of CADR can be due to any of the drugs. This makes identification of the offending drug a major challenge.

RECHALLENGE FOR FIRST-LINE DRUGS OR USE SECOND-LINE REGIMEN

The use of rifampin and isoniazid in any treatment regimen for tuberculosis is associated with superior outcomes.¹⁵ The limited numbers of effective antituberculosis drugs and significant toxicities of the less effective second-line drugs, create a clinical management dilemma when first-line drugs cannot be used. There is abundant data that outcomes are sub-optimal when using second-line drugs in drug resistant tuberculosis.¹⁶ Less is known about the outcomes of using second-line drugs in non-drug resistant tuberculosis. In a well-designed study, Suárez et al. showed that mortality, cure rates and compliance were all unfavourable when using second-line antituberculosis drugs, compared to standard therapy in a Peruvian population. This cohort included patients who had a failed response to first-line regimen and did not have drug resistant tuberculosis.¹⁷

The risks of tuberculosis-associated mortality, drug resistance, transmission of tuberculosis by infectious patients to other patients, staff and the community need to be balanced against the risk of a disabling or fatal rechallenge reaction. It has previously been shown that diagnostic rechallenge to pinpoint the offending drug is feasible and safe.¹⁸ The safety of diagnostic rechallenge was further confirmed in the rechallenging of more than 150 cases of antituberculosis drug-associated CADR.^{18,19} There were no long-term morbidities or deaths as a



Figure 4: Ongoing Lichenoid Drug Eruption during tuberculosis treatment

direct result of a rechallenge reaction. However, this was under close supervision in a hospital and an experienced multidisciplinary team managed the patients. Based on these data, tuberculosis outcomes are likely to be better if a rechallenge is undertaken and only the offending drug is removed from the treatment regimen.

MULTIDISCIPLINARY APPROACH

Tuberculosis-associated CADRs are multi-organ diseases that often require expertise ranging from hepatologists, infectious disease specialists, pulmonologists, dermatologists, dietitians and others. The best outcomes are attained using a multidisciplinary approach.

HOW SOON CAN RECHALLENGE BE INITIATED?

In tuberculosis treatment, interruption of therapy during the intensive phase is associated with a three times higher risk of death. The risk is even higher in HIV-infected persons.^{20,21} This suggests that re-initiating therapy as soon as possible is advisable considering the relative safety of rechallenging.

ROLE OF *IN-VITRO*, PATCH AND SKIN PRICK TESTS

There is limited data on the efficacy of *in-vitro* tests to identify offending antituberculosis drugs. They are technically demanding, require expensive equipment and sterile cultures. These factors make them inaccessible, especially in resource-poor settings where tuberculosis is most prevalent.⁴ The role of patch, skin prick and intradermal testing is yet to be fully determined for antituberculosis drug-associated CADR. The specificity and sensitivity of these tests is dependent on the phenotype of CADR, the drug being tested and the vehicle carrying the test drug.^{22,23} It has recently been shown that in HIV-infected persons, patch and skin prick tests to antituberculosis drugs resulted in systemic reactions rather than localised reactions. The tests had low sensitivity. Using the Common Terminology Criteria for Adverse Events (CTCAE), a validated score used to grade adverse reactions, there was no difference in severity of rechallenge reactions resulting from patch



Figure 5: Bullous Fixed Drug Eruption

tests, skin prick tests and oral rechallenge, with the offending drug.^{19,24,25} This suggests that in HIV-tuberculosis co-infection, cutaneous tests may not be beneficial in reducing the risk of rechallenge reactions.

ORAL PROVOCATION TESTING

Oral drug provocation tests are still considered the gold standard to identify the offending drug.²⁶ The risk of a rechallenge reaction must be balanced against the morbidity and mortality associated with sub-optimal therapy. There are few aspects of diagnostic oral rechallenge that are not fully defined. These include the use of bridging therapy before initiating rechallenge, whether rechallenge should occur at full dose or with incrementally increasing doses and the sequence in which the drugs are rechallenged.⁴

BRIDGE THERAPY BEFORE RECHALLENGE

To avoid mono-therapy and to minimise the risk of developing mycobacterial resistance during the prolonged rechallenge process with the individual drugs, a bridging therapy of three second-line drugs, to which the patient has not previously been exposed, is advised. The selection of drugs depends on local treatment guidelines, availability, toxicities and underlying co-morbidities. It has been established that almost a quarter of HIV infected patients with tuberculosis associated CADR develop multiple drug hypersensitivity to both first and second-line drugs. If rechallenge with first-line drugs is initiated too early, the overlapping clinical features of the rechallenge reactions and adverse reactions to the bridge therapy create confusion. Reactions to the bridge therapy usually develop within two weeks of their initiation. Based on this, it is recommended that rechallenge should only be undertaken two weeks into the bridge therapy.²⁷

THE SEQUENCE OF DRUGS TO RECHALLENGE

Some authors believe that the most effective drugs, namely rifampicin and isoniazid, should be rechallenged first to minimise the risks of suboptimal therapy during the prolonged rechallenge process. Others suggest that the drugs least likely to cause a reaction should be rechallenged first.⁴ It is well established that all first-line drugs cause CADR but there are no good studies quantifying the contribution of each drug. Thus, it is suggested to rechallenging with isoniazid and rifampicin first to minimise risk of developing drug resistant strains of tuberculosis, currently a major public health problem.

ESCALATING VERSUS FULL DOSES IN RECHALLENGING

In drug-induced hepatitis, Sharma et al. have shown that the severity and frequency of rechallenge reactions was not different when comparing full dose or incremental rechallenge.²⁸ There is currently no robust data supporting the safety of either method in CADR. Thus, it is suggested that dosing be escalated in rechallenge as recommended in the American Thoracic Society guidelines for reintroduction of antituberculosis drugs following drug-induced hepatitis.²⁹ An ongoing study to answer this question is currently underway.¹⁹

INTERVAL BETWEEN RECHALLENGING WITH FIRST-LINE DRUGS

The interval between the sequential reintroduction of the individual drugs is not well established. In an ongoing study it has been established that >90% of rechallenge reactions occur within 72 hours. Based on this, rechallenging with a new first-line drug every 96 hours is recommended while monitoring closely for features of a rechallenge reaction. The features of a rechallenge reaction in these studies was a variable combination of erythema, rash, pruritus, transaminitis, eosinophilia, fever, oedema and nausea.^{18,19}

DURATION OF THERAPY AND FINAL TREATMENT REGIMEN

This depends on the offending drug(s), duration of treatment before interruption, drug sensitivities, co-morbidities and other drugs the patient is using. It is a complicated process requiring expert opinion, preferably by an infectious diseases specialist with experience in managing tuberculosis.

MANAGEMENT OF LICHENOID DRUG ERUPTIONS

Due to the lack of acute markers, it is difficult to pinpoint the offending drug in LDE. As a result, in HIV-infected patients the approach is to continue treatment under cover of potent topical steroids and phototherapy. However, this carries a risk of permanent dyspigmentation and should be discussed in detail with the patient and co-managed with a dermatologist.^{30,31}

CONCLUSION

Tuberculosis is currently a major public health challenge. It is largely driven by the HIV pandemic. Tuberculosis

and HIV co-infection is associated with an increased risk of CADR. This often creates major challenges in the diagnosis and management of CADR, identification of the offending antituberculosis drug and selection of subsequent therapy for tuberculosis. Clinical subtypes of tuberculosis-associated CADR present different diagnostic and management challenges and clinicians should be able to identify each.

Elimination of first-line drugs results in poorer outcomes in the management of tuberculosis. This is even more

so in HIV-tuberculosis co-infection. Thus, a diagnostic rechallenge following antituberculosis-associated CADR is often advisable to eliminate the offending drug from the treatment regimen. It has previously been shown that diagnostic rechallenge is safe and feasible in a controlled environment. However, rechallenge is associated with multiple pitfalls that need careful consideration before it can be attempted. With a rational multidisciplinary approach, outcomes in antituberculosis-associated CADR can be improved considerably.

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