

Therapeutic Trial of Rifabutin After Rifampicin-Associated DRESS Syndrome in Tuberculosis-Human Immunodeficiency Virus Coinfected Patients

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Elimination of a rifamycin from the treatment regimen for tuberculosis negatively impacts outcomes. Cross-reactivity between the rifamycins after drug eruptions is unclear. We report 6 consecutive human immunodeficiency virus-infected patients with rifampicin-associated drug rash with eosinophilia and systemic symptoms (DRESS) syndrome confirmed on diagnostic rechallenge. The patients subsequently tolerated rifabutin. These data inform clinical management of tuberculosis-associated drug reactions.

Keywords. alternative; rifabutin; rifampicin-associated drug eruption; tuberculosis HIV coinfection.

Tuberculosis (TB) is a major cause of mortality in sub-Saharan Africa [1]. The upsurge in the incidence of TB in recent years has been driven by the human immunodeficiency virus (HIV) pandemic. In 2013, 61% of new cases of TB in South Africa were coinfecting with HIV [2]. Cutaneous adverse drug reactions (CADRs) are generally more common in persons infected with HIV, including those associated with 1st-line anti-TB drugs (FLTDs) [3].

All FLTDs can cause a wide variety of CADRs, including drug rash with eosinophilia and systemic symptoms (DRESS syndrome), a severe form of CADR with mortality of up to 10% [4]. The diagnosis of DRESS syndrome warrants interruption of treatment that may impact cure and survival [3]. We have previously shown that diagnostic rechallenge in the context of

FLTD, even in severe CADR such as DRESS syndrome and toxic epidermal necrolysis, is usually successful, and the majority of rechallenge reactions are nonlife threatening. Rechallenge facilitates detection of the offending drug allowing its removal from the treatment regimen while retaining the other FLTD within the treatment regimen [5]. This improves outcomes in the management of TB, because 2nd-line drugs are less efficacious and are associated with higher toxicity profiles [3].

The rifamycins are a class of synthetic antibiotics particularly effective against mycobacteria. Rifampicin, rifabutin, rifapentine, and rifaximin are the currently available rifamycins. Their inclusion in the treatment regimen for TB has been shown to shorten the duration of therapy, improve cure rates, and lower relapse rates [6]. Thus, elimination of rifampicin in the context of CADR often impacts negatively on treatment outcomes. For that reason, it would be useful if rifampicin could be substituted with an alternative rifamycin.

However, there are limited data about the cross-reactivity among the rifamycins in the context of CADR. We report the successful switch to rifabutin as an alternative to rifampicin in a series of patients with rifampicin-associated DRESS syndrome.

METHODS

The subjects included in this study had initially presented to the dermatology ward at Groote Schuur Hospital, a tertiary center in Cape Town, South Africa, with CADR while on FLTDs between November 2013 and June 2015. They were all enrolled in a larger randomized controlled trial comparing sequential, additive, and incremental dosing versus sequential, additive, and full therapeutic dose reintroduction of FLTD in CADR. That study, now completed, was approved by the institutional Human Research Ethics Committee (Reference: 246/2009). The methods used in the parent study have previously been described [7, 8]. Eighty-eight patients were rechallenged with rifampicin in the parent study, and 19 of 88 (22%) patients reacted to rifampicin. Based on recently published literature, the last 6 consecutive cases of the 19 who reacted to rifampicin were switched to rifabutin [9, 10].

On admission, the anti-TB drugs were stopped when TB-associated CADR was suspected. Before rechallenge, all patients were investigated to confirm active TB. Once the CADR had resolved and laboratory parameters returned to baseline, three 2nd-line anti-TB drugs (SLTDs) to which the patient has not previously been exposed were initiated as bridge therapy. This was to minimize the risk of developing mycobacterial resistance during the prolonged rechallenge process with the individual drugs. This was followed by a diagnostic workup (patch testing

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Table 1. Demographic and Clinical Characteristics of Six Cases of Tuberculosis-Associated DRESS That Developed Rechallenge Reactions to Rifampicin and Tolerated Rifabutin

Case	Age in Years	Gender	CD4 Count (Cells/mm ³)	ARV	Feature of DRESS at Initial Presentation	1st-Line Agents Rechallenged	2nd-Line Agents Used	Hypersensitivity Reactions to 1st- and/or 2nd-Line Agents	CTCAE Criteria Severity Grading of Rechallenge Reaction to 1st-Line Agents
1	36	M	63	Yes	Rash, eosinophilia, oedema, >38°C, ALT > 5 × ULN, lymphadenopathy	RIF, INH, PZA, ETH	MOX, ETH, KNM	RIF: itch, morbilliform rash, hepatitis eosinophilia, INH: hepatitis, eosinophilia	Moderate
2	23	F	401	No	Rash, eosinophilia, oedema, fever >38°C, ALT > 5 × ULN, lymphadenopathy	RIF, INH, PZA, ETH	MOX, ETH, KNM, CPM,	RIF: itch, morbilliform rash, hepatitis, eosinophilia, oedema MOX: morbilliform rash, hepatitis, oedema, fever, nausea, vomiting	Mild
3	31	F	457	No	Rash, atypical lymphocytes, oedema, fever >38°C, ALT > 2 × ULN, lymphadenopathy	RIF, INH, PZA, ETH	MOX, ETH, KNM TER,	RIF: itch, morbilliform rash, hepatitis, eosinophilia MOX: intense itch morbilliform rash, fever,	Mild
4	35	F	74	No	Rash, eosinophilia, oedema, fever >38°C, ALT > 5 × ULN, lymphadenopathy	RIF, INH, PZA, ETH	MOX, ETH, KAN	RIF: itch, morbilliform rash, oedema, INH: hepatitis, fever, nausea, diarrhoea	Mild
5	49	M	32	No	Rash, eosinophilia, oedema, fever >38°C, ALT > 5 × ULN, lymphadenopathy	RIF, INH, PZA, ETH	MOX, TER, KAN, ETH	RIF: morbilliform rash, eosinophilia, fever, diarrhoea, hypotension MOX: eosinophilia, fever, diarrhea	Severe
6	44	F	153	Yes	Rash, eosinophilia, anaemia, oedema, fever >38°C, ALT > 5 × ULN, lymphadenopathy	RIF, INH, PZA, ETH	MOX, TER, KAN, ETH	RIF: itch, morbilliform rash, hepatitis eosinophilia, oedema PZA: itch morbilliform rash, MOX and/or TER and/or ETH: itch, erythematous rash, hepatitis, oedema, eosinophilia	Moderate

Abbreviations: ALT, alanine aminotransferase; AMK, amikacin; ARV, antiretroviral therapy; CADR, cutaneous adverse drug reactions; CPM, capreomycin; CTCAE, common terminology criteria for adverse events (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening; grade 5, death); DRESS, drug rash with eosinophilia and systemic symptoms; EMB, ethambutol; ETH, ethionamide; INH, isoniazid; KNM, kanamycin; MOX, moxifloxacin; PZA, pyrazinamide; RIF, rifampicin; TER, terizidone; ULN, upper limit of normal.

followed by a skin prick test and an oral rechallenge) to pinpoint the offending FLTD. Depending on the sensitivities of the patient's strain of TB, isoniazid followed by rifampicin, pyrazinamide, and ethambutol were reintroduced consecutively and additively. A rechallenge reaction after any of these modalities lead to immediate withdrawal of the drug from the treatment regimen. The last 6 cases of the study that developed rechallenge reactions to rifampicin were switched to oral therapeutic dose of rifabutin after completion of the rechallenge process. The other FLTD that did not induce a rechallenge reaction were continued uninterrupted. Laboratory parameters and clinical features usually associated with a drug reaction were closely monitored for 96 hours after initiating rifabutin.

RESULTS

The demographic and clinical characteristics of the 6 patients with DRESS syndrome that developed rechallenge reactions to rifampicin and subsequently tolerated rifabutin are summarized in Table 1. All 6 participants were TB and HIV coinfecting (median CD4 count 111 cells/mm³). Three of them had pulmonary TB and 3 had disseminated disease. One had previous TB before

the current episode, and none had a previous drug reaction. Five of the 6 participants were determined not to be resistant to rifampicin by GeneXpert MTB/RIF assay before they were started on anti-TB therapy. Two were on antiviral therapy (ART), which was initially interrupted but reinitiated uneventfully. Four of the 6 were on co-trimoxazole for *Pneumocystis jiroveci* pneumonia prophylaxis at the onset of CADR, which was stopped and not reinitiated. All 6 fulfilled the diagnostic criteria of DRESS syndrome at initial presentation as defined by Bocquet et al [11].

The rechallenge reactions to rifampicin were characterized by a rash in 6 of 6 (100%), itch and eosinophilia in 5 of 6 (83%) each, hepatitis in 4 of 6 (67%), edema in 3 of 6 (50%), and fever, hypotension, and diarrhea once. They were treated with potent topical steroids until resolution. None received systemic steroids. All 6 cases developed multiple drug hypersensitivity to at least 2 anti-TB drugs (Table 1). Three of the 6 cases reacted to 2 FLTD and required more than the standard 6 months of treatment. The other 3 reacted to rifampicin and at least 1 SLTD, but they were successfully rechallenged with the other 3 FLTDs (isoniazid, pyrazinamide, and ethambutol). Consequently, the

latter 3 cases needed standard 6 months of TB treatment after successful replacement of rifampicin with rifabutin.

DISCUSSION

We report successful switch to rifabutin as an alternative to rifampicin in 6 consecutive cases of rifampicin-associated DRESS syndrome, effectively normalizing the duration of therapy. The major concern in rechallenging with structurally similar drugs is the possibility of cross-reactivity. Cross-reactivity in DRESS syndrome is well described for several structurally similar compounds such as aromatic anticonvulsants and sulfonamide antibiotics, the latter particularly in persons infected with HIV [12]. However, there have been reports of successful switch to rifabutin in rifampicin-associated hepatotoxicity and hypersensitivity reactions, although a significant proportion reacted to both drugs [9, 10, 13]. Our findings suggest that the 2 drugs in HIV-infected persons with DRESS may not cross-react in the context of DRESS. It is still unknown whether this applies to Stevens Johnson syndrome and lichenoid drug eruption, other forms of CADR associated with FLTD [3]. Larger studies are needed to confirm these findings.

A systematic review by Davies et al [14] found no significant differences in cure rates, relapse rates, and adverse event profiles between those receiving either one of the 2 rifamycins, rifampicin or rifabutin, in their treatment regimen. The 2 drugs have a comparable efficacy in the treatment of TB in persons infected with HIV [15]. However, drug interactions between rifabutin and ART have to be considered in this subgroup. Efavirenz, which forms the backbone of 2nd-line ART regimen in South Africa, significantly reduces plasma levels of rifabutin. Thus, higher doses of rifabutin are required when the drug is used with efavirenz [16]. We used this higher dosing in all of our 6 patients who also initiated an efavirenz-containing regimen. The switch to rifabutin in our patients facilitated an optimal treatment regimen despite the loss of an important FLTD.

Cross-resistance between the 2 rifamycins, estimated to go up to 90%, is another concern in re-exposing a patient to a potentially life-threatening rechallenge reaction [17]. Therefore, it is prudent to ascertain that rifampicin-sensitive strains of TB are being treated, as was the case in 5 of our cases. The other case with disseminated disease was initiated on therapy based on clinical features only.

The major limitation of our study is the small sample size. Confirmation of rifampicin-associated DRESS syndrome by diagnostic rechallenge is still infrequently performed considering the severity of the reaction. Larger studies in multiple centers are needed to confirm our findings. It is also not clear whether

these findings are applicable in non-HIV-infected persons or other severe forms of CADRs.

CONCLUSIONS

In summary, we show that rifabutin is a viable replacement in rifampicin-associated DRESS syndrome in patients coinfecting with TB and HIV. Our findings, if confirmed in larger cohorts and different clinical settings, will allow patients with rifampicin-associated DRESS to remain on optimum treatment, improving cure rates and compliance.

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