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Short Communication

High rate of adverse drug reactions with a novel tuberculosis re-treatment regimen combining triple doses of both isoniazid and rifampicin ☆

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ABSTRACT

Objectives: High-dose rifampicin (R) and isoniazid (H) are known to be safe but were not yet combined in a single regimen. The primary objective of the TRIple-DOse RE-treatment (TRIDORE) study is to determine whether a 6-month firstline regimen with triple dose of both R and H (intervention arm; $6R^3H^3ZE$) is non-inferior in terms of safety compared to a normal-dose regimen (6RHZE) in previously treated patients with R-susceptible (Rs) recurrent tuberculosis (TB).

Design/methods: TRIDORE is an ongoing pragmatic open-label multi-stage randomized clinical trial.

Results: Between March 2021 and February 2022, 127 consenting patients were randomly assigned to either the intervention or control arm: 62 and 65 were treated with $6R^3H^3ZE$ and 6RHZE, respectively. Of 127, 111 (87.4%) were male and the median age (interquartile range) was 37 (30-48) years. The median body mass index at enrollment was 18.1 (16.3-19.7) kg/m^2. Drugrelated severe adverse events (AEs) (grade III-V) were significantly more frequent when $6R^3H^3ZE$ was used (5/62 vs 0/65, $P = 0.03$, difference weighted for site 8% [95% confidence interval: 1.0,14.3]). The Data and Safety Monitoring Board recommended publishing our interim safety data analysis.

Conclusion: We show that the combination of triple-dose R with triple-dose H in a re-treatment regimen for patients with Rs-TB causes excess drug-related AEs.

Introduction

Worldwide, tuberculosis (TB) continues to be a major cause of mortality [1]. Rifampicin (RMP, R) and isoniazid (INH, H) are the two most powerful first-line anti-TB drugs. In patients never treated for TB, both drugs are combined with ethambutol (E) and pyrazinamide (Z) to constitute the 6-month category I first-line regimen (2 months RHZE and 4 months RH). However, about 10% will have recurrent TB (treatment failure of the first treatment, relapse, or treatment after being lost to follow-up) [1]. Patients with recurrent TB are more at risk of having TB that is resistant to first-line drugs, either present from the start of category I treatment or acquired during treatment [2]. Drug susceptibility testing (DST) for at least R is recommended to inform the choice of re-treatment regimen [3]. Usually, Xpert MTB/RIF (a molecular assay that detects TB and RMP resistance) is used. Since 2018, the World Health Orga-

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Table 1
Methods - TRIDORE trial

	Intervention arm (Triple-dose RMP and INH)	Control arm (Normal-dose)
Design	Pragmatic open-label multi-stage randomized clinical trial	
Study population and inclusion/ exclusion criteria	Patients with rifampicin-susceptible recurrent smear-positive tuberculosis Inclusion criteria: • All newly registered patients with smear-positive recurrent pulmonary TB • Adults as well as children (no age limit) • HIV-negative as well as HIV-positive • Able and willing to provide written informed consent Exclusion criteria: • All patients with TB initially resistant to rifampicin will be referred for multi-drug resistant TB treatment and will not be included • Patients transferred at time of diagnosis to a health facility not supported by Damien Foundation will be excluded • Patients previously enrolled in the trial and with another episode of rifampicin-susceptible TB during the study period • Those with grade III elevation of liver function tests at baseline, or grade II elevation with clinical signs of active liver disease at screening • Pregnant or breastfeeding woman • HIV co-infected patients requiring treatment with a protease inhibitor	
Setting	Nine Niger National Tuberculosis Program clinics	
Randomization	1:1 ratio	
Treatment duration	6 months	
Regimen	R^3H^3ZE	RHZE
Drugs dosage	R (30 mg/kg) H (15 mg/kg) Normal-dose Z and E	Normal-dose R, H, Z, and E
Drugs supplemented	Pyridoxine (vitamin B6)	-
Adherence and follow-up of safety and treatment response.	As per routine practice, during treatment patients are in daily contact with the direct observed therapy, and minimally monthly clinic visits are scheduled for monitoring of safety and treatment response. Six months and one year after treatment completion or cure the patient will be checked for relapse with systematic sputum acid-fast bacilli-microscopy and TB culture.	
(S)AE collection	Systematic alanine transaminase assessments (at baseline, after 2 weeks of treatment, and every month until month 4 of treatment) and Hepatitis B and C testing in case of hepatotoxicity and/or jaundice. Adverse events and their grading and dates of occurrence were reported on the treatment cards.	
Primary endpoint	The primary objective is to study if a high-dose first-line regimen is non-inferior to the same regimen at regular dosing in terms of safety, in previously treated patients with rifampicin-susceptible-TB on Xpert MTB/RIF. The primary safety endpoint was “any grade III-V AE during treatment, assessed as probably or definitely related to TB treatment”. Secondary safety endpoints are “drug-induced hepatotoxicity”, “any TB treatment change due to drug-induced hepatoxicity”, “any TB treatment change due to AE”, “any grade III-V AE”, and “any SAE”.	
Statistics	Safety analysis population includes all patients enrolled and allocated to a treatment regimen and who took at least one dose of the study drug. Analysis is done according to the treatment regimen truly received. The primary and interim analysis includes the calculation of the risk difference (95% confidence interval) for safety (pair-wise comparison between treatment arms). The analysis is performed using a generalized linear model with Bernoulli error distribution and identity link. The model includes fixed effects for site and treatment group. Based on the regression coefficient of this model, a two-sided confidence interval is calculated for the difference in probability of experiencing the primary safety endpoint ($6R^3H^3ZE$-6RHZE). If this confidence interval would lie entirely below 10%, then the high-dose regimen would be non-inferior to the control regimen; else non-inferiority cannot be established. For the protocol-defined interim analysis, we first calculated a 40% confidence interval (more narrow, thus less likely to exceed 10%, the non-inferiority margin, to avoid a too high risk of making a type 1 error and thus prematurely abandoning a potentially effective high-dose regimen). As both the Trial Management Group and the Data Safety Management Board agreed to stop enrollment in the high-dose arm, the interim analysis was also the final analysis, and also 95% confidence intervals were calculated using the same data.	

[3], triple dose; AE, adverse event; E, Ethambutol; HIV, human immunodeficiency virus; INH/H, isoniazid; RMP/R, rifampicin; S, severe; TB, tuberculosis; Z, Pyrazinamide.

nization guidelines also recommend INH and fluoroquinolone (FQ) DST, including in previously treated patients with RMP-susceptible TB (Rs-TB). In patients diagnosed with H-resistant (Hr)/Rs-TB, a 6-month regimen is recommended that combines first-line drugs (RZE) with a potent second-line TB drug, levofloxacin (a FQ). However, in most low- and middle-income countries, access to INH and FQ DST remains limited, albeit less so with the roll-out of 10-color Xpert MTB/XDR®. Most patients with recurrent Rs-TB are repeatedly treated with category I [4]. In some settings, levofloxacin is empirically (without guidance by DST) added to first-line drugs to constitute a more powerful re-treatment regimen for Rs-TB. However, adding a single second-line drug, levofloxacin, to previously unsuccessful first-line drugs, may result in acquired FQ resistance because some *rpoB* mutations are systematically missed by Xpert MTB/RIF [5]. Patients diagnosed with Rs-TB may still have RMP-resistant TB (Rr-TB).

Ideally, a first-line Rs-TB re-treatment regimen in settings with poor access to INH and FQ DST should be robust enough to overcome any detected or undetected initial INH resistance without adding a second-line drug. Six months with the four first-line drugs throughout had already been shown to be both safe and effective for patients with Hr/Rs-TB [6,7]. High-dose R [8,9] and H [10,11] are known to result in a better treatment response and up to triple dosing was safe for both drugs [12]. However, no previous study assessed the efficacy and safety of the combination of triple-dose INH (15 mg/kg daily) combined with triple-dose RMP

Table 2
Interim safety results of a triple-dose versus normal-dose first-line regimen.

	Triple-dose RMP and INH (N = 62)		Normal-dose (N = 65)			% difference between intervention and control[d]		
	n	(%; 95% CI)	n	(%; 95% CI)	*P*-value[b]	%	(40% CI)	(95% CI)
Primary endpoint								
Grade III-V drug-related AEs[a]	5	(8.1; 3.5,17.5)	0	(0.0; 0.0,5.6)	0.03	8	(5.9,9.4)	(1.0,14.3)
Secondary endpoints								
Any AE (regardless of grading/relationship with TB drugs)	18	(29.0; 19.2,41.3)	11	(16.9; 9.7,27.8)	0.1	11	(7.6,15.0)	(-2.6,25.1)
Grade III-V AEs (regardless of relationship with TB drugs)	11	(17.7; 10.2,29.0)	2	(3.1; 0.9,10.5)	0.008	14	(11.1,16.5)	(3.7,24.0)
Any serious AEs	11	(17.7; 10.2,29.0)	2	(3.1; 0.9,10.5)	0.008	14	(11.1,16.5)	(3.7,24.0)
Treatment change (any reason)	7	(11.3; 5.6,21.5)	0	(0.0; 0.0,5.6)	0.006	11	(8.8,13.0)	(3.1, 18.7)
Death	4	(6.5; 2.5,15.4)	1	(1.5; 0.3,8.2)	0.2	5	(2.8,6.5)	(-2.2,11.6)
Hepatotoxicity[c]	4	(6.5; 2.5,15.4)	0	(0.0; 0.0,5.6)	0.05	6	(4.6,7.8)	(0.1,12.3)
ALT grade I or II increase without jaundice	7	(11.3; 5.6,21.5)	4	(6.2; 2.4,14.8)	0.4	5	(2.8,7.7)	(-4,14.5)

AE, adverse event; ALT, alanine transaminase; CI, confidence interval; INH, isoniazid; RMP, rifampicin; TB, tuberculosis.
[a] Assessed as probably or definitively related
[b] Fisher's exact test
[c] Grade III or higher increase of ALT, or grade II increase with jaundice
[d] Weighted for treatment site. The 40% CI is shown, as planned in the statistical analysis plan, thus more narrow than 95% CI, to avoid a too high risk of making a type I error and thus prematurely abandoning a potentially effective high-dose regimen. To be non-inferior, the upper bound of the 40% CI around the difference should be below the 10% non-inferiority margin, as pre-defined in the study protocol. For endpoints with the upper bound of the CI larger than 10%, non-inferiority was not shown. Considering that the present interim analysis was also final, as the high-dose regimen was interrupted, post-hoc we also decided to calculate 95% CI.

(30 mg/kg daily). The primary objective of the TRIple-DOse RE-treatment (TRIDORE) study is to determine whether a 6-month first-line regimen with triple dose of both RMP and INH is non-inferior (10% margin) in terms of safety compared to a normal-dose regimen in previously treated patients with recurrent Rs-TB. Here we report interim findings.

Methods

TRIDORE (Clinicaltrials.Gov. = NCT04260477; ethics approval by University of Antwerp (20/12/140) and Niger (067/2020/CNERS) Ethics Review Boards) is an ongoing pragmatic open-label multi-stage randomized clinical trial in nine Niger National Tuberculosis Program clinics supported by the Damien Foundation, a Belgian non-governmental organization (NGO).

Consenting participants with recurrent smear-positive Rs-TB were 1:1 randomly assigned to either the intervention arm (6 months of R^3H^3ZE; R^3 at 30 mg/kg, H^3 at 15 mg/kg, and normal-dose pyrazinamide and ethambutol, supplemented with pyridoxin) or the control arm (6RHZE). In addition to routine monitoring, liver function tests (alanine transaminase) were performed at fixed intervals. The primary safety endpoint was the occurrence of any grade III-V adverse event (AE), estimated to be likely or definitively related to TB drugs (Table 1).

Results

Between March 2021 and February 2022, 127 patients were enrolled, of whom 62 and 65 were treated with $6R^3H^3ZE$ and 6RHZE, respectively. Baseline characteristics were similar between both arms. Of 127, 111 (87.4%) were male and the median age (interquartile range) was 37 (30-48) years. Co-infection with HIV, hepatitis B, and/or hepatitis C was present in 3 (2.4%), 13 (10.2%), and 3 (2.4%) patients, respectively. The median body mass index at enrollment was 18.1 (16.3-19.7) kg/m^2.

Grade III-V drug-related AEs were significantly more frequent when the triple-dose regimen was used (5/62 vs 0/65, $P = 0.03$, difference weighted for site 8%; 95% confidence interval: 1.0,14.3), with four of five grade III-V drug-related AEs being due to hepatitis (Table 2).

Discussion

Our interim analysis showed that grade III-V drug-related AEs occurred more frequently when a re-treatment regimen with both triple-dose RMP and INH was used in patients with Rs-TB. While in patients treated with the normal-dose control regimen AEs (any, regardless of grading or relationship with TB drugs) were reported in 16.9% (11/65), only 3.1% (2/65) experienced grade III-V AEs, which were all reported as unrelated to treatment. This contrasted with 17.7% (11/62, with 5/11 being drug-related) of grade III-V AEs among those treated with the high-dose regimen. Especially hepatotoxicity, which can be caused by both H and R [13], was more frequent among those treated with the high-dose regimen (4/62 vs 0/65, $P = 0.05$). There were four deaths in the high-dose group, none of which were reported as likely or definitely related to TB treatment. Still, considering the significantly higher proportion of patients who had to interrupt treatment because of drug-related grade III-V AEs, we recommend not systematically using both triple-dose RMP and INH in a re-treatment regimen for patients with Rs-TB.

Based on our interim findings and advice from the Data and Safety Monitoring Board (DSMB), with whom we discussed all severe AEs (SAEs) and the relationship between any grade III-V AEs and the prescribed TB drugs, we stopped enrolling on the high-dose regimen, while we continue enrollment and the evaluation of 6RHEZ as normal-dose re-treatment regimen for Rs-TB. Indeed, according to our interim analysis, 6RHEZ was safe, without drug-related severe AEs in our cohort of 65 patients. If also effective in terms of achieving relapse-free cure, we will propose to use this regimen, instead of category I, for patients in need of a re-treatment regimen for Rs-TB. With ethambutol and pyrazinamide throughout, it may be more active than category I (uses ethambutol and pyrazinamide only in the first 2 months), especially in patients with Hr/Rs-TB.

The unexpectedly higher rate of SAEs in the intervention arm prompted us to interrupt enrollment, thus conducting our analysis using data from a relatively small cohort of 127 patients. The control arm, in contrast, did better than expected. As we prematurely stopped enrollment on the high-dose regimen, and with only 127 instead of the planned 362 patients randomized, we will probably not have enough power to identify whether there is a difference between both regimens in terms of our primary efficacy endpoint,

relapse-free cure. In contrast, after ethics approval, we continue enrolling on the normal dose. We will be able to show whether this regimen using the four first-line drugs throughout results in high levels of relapse-free cure, without acquired resistance to R. The strength of our study is the pragmatic trial design, with randomized allocation of patients to study regimens in routine care. Moreover, all grade III-V AEs and SAEs were exhaustively and regularly discussed with both the Trial Management Group and the DSMB, to establish the relationship between AEs and TB treatment. A weakness is the lack of blinding. Information bias may have occurred when clinicians evaluated safety events.

In conclusion, the combination of triple-dose RMP with triple-dose INH in a re-treatment regimen for patients with Rs-TB causes excess drug-related AEs and is not recommended. The control regimen, with four first-line drugs throughout 6 months, is safe. If also effective, it may be an alternative re-treatment regimen for patients with Rs-TB, including those with baseline resistance to H.

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Ethical approval

The study was approved by the Niger National Ethics Committee, University of Antwerp, and the Institute of tropical medicine's (ITM) Institutional Review Board.

Author contributions

SMB, PA, and DT designed the study. TA and DT did the analysis. SMB and DT wrote the first draft. All co-authors contributed to the interpretation of the findings, critically revised subsequent versions, and approved the final version.

Declarations of competing interest

The authors have no competing interests to declare.

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