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Early View

Research letter

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Bedaquiline can act as core drug in a standardized treatment regimen for fluoroquinolone-resistant rifampicin-resistant tuberculosis

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Take home message (256 of max 256 characters, including spaces)

In the original short treatment regimen for rifampicin resistant tuberculosis bedaquiline proved an adequate core drug for fluoroquinolone resistance, ensuring early conversion and relapse-free cure. The use of linezolid did not have the same early effect.

Plain Language Summary

Previous studies showed that a fluoroquinolone-based short treatment regimen is effective for the treatment of tuberculosis (TB) resistant to the most important first-line TB drug, rifampicin. How to replace the fluoroquinolone in case of resistance to fluroquinolone, the most potent second-line drug, is unknown. Our findings show that replacing a fluoroquinolone by bedaquiline in the same short treatment regimen resulted in an early and sustained treatment response. When linezolid was used to the strengthen the fluoroquinolone-based regimen during the first treatment months the same early effect was not shown. Our findings suggest that bedaquiline, but probably not linezolid, can act as the treatment's core drug and can assure relapse-free cure.

To the editor

In Bangladesh, a standardized short treatment regimen (STR) was highly effective in patients diagnosed with rifampicin-resistant-tuberculosis (RR-TB), without proof of initial resistance to fluoroquinolone, and no prior treatment for RR-TB.[1] The STR relied on a fluoroquinolone, either gatifloxacin, levofloxacin, or moxifloxacin, as core drug, with gatifloxacin being most effective in assuring relapse-free cure.[2] A second-line injectable was used during at least the first four months to prevent the selection of fluoroquinolone-resistant (sub-)populations.[3] Other drugs served as companion drugs.

Up to now, there is little evidence on effective standardized short treatment for fluoroquinolone-resistant RR-TB [4]. Before bedaquiline was available in Bangladesh, in patients with initial resistance to fluoroquinolone but susceptibility to kanamycin on rapid local phenotypic drug susceptibility testing (DST), [5] both linezolid (L) and high-dose gatifloxacin (G) were added to the same background regimen (components: K=kanamycin, Et=ethionamide, Hh=high-dose isoniazid, C=clofazimine, E=ethambutol, and Z=pyrazinamide) to constitute a linezolid-strengthened STR (LZD/GFX-STR: 2LGKPtHhCEZ/ 2GKPtHhCEZ/ 5GCEZ). Once bedaquiline (B) became available, it was added to the background regimen to constitute a bedaquiline-based STR (BDQ-STR: 4BKPtHhCEZ/ 5BCEZ). In the first regimen, gatifloxacin was still included. High-dose fluoroquinolones can overcome fluoroquinolone resistance when the level of resistance is not high [6]. Linezolid (600 mg), since recently categorized as a "group A" by the World Health Organization, was added to increase the bactericidal and sterilizing activity of the regimen [7]. In the second regimen, bedaquiline – a drug with high bactericidal and high sterilizing activity – replaced the fluoroquinolone as core drug and was used throughout treatment [8]. All RR-TB patients started on either LZD/GFX-STR or BDQ-STR were studied. A posteriori reference DST for second-line drugs was done either in Bangladesh or at the Supranational Reference Laboratory in Antwerp. Initial fluoroquinolone resistance was categorized as 'high-level' if the minimum inhibitory concentration (MIC) for GFX was 2 mg/L or higher on Löwenstein-Jensen, or ofloxacin 8 mg/L on agar. Mutation analysis was performed using

whole-genome or Sanger sequencing. Methods used are described elsewhere [9]. All patients starting any STR regimen provided written informed consent. Ethics approval for the present deidentified analysis was provided by the Institute of Tropical Medicine institutional review board (1233/88).

The table shows all 21 patients treated with either a LZD/GFX-STR or BDQ-STR. Two patients with fluoroquinolone-susceptible RR-TB and treated for the first time with a second-line gatifloxacin-based regimen (LZD/GFX-STR) were excluded. In both, the effect of strengthening the STR with LZD could not be assessed as gatifloxacin was still a fully active core drug and drove relapse-free cure. One patient treated with the BDQ-STR had fluoroquinolone-susceptible RR-TB. Here the presence or absence of initial resistance to fluoroquinolone did not affect the treatment outcome, as no fluoroquinolone was included in the BDQ-STR. This patient was not excluded from further analysis. Another patient was excluded because the bacteriological effect of BDQ-STR could not be assessed. After a good initial response with culture conversion at month 1, this patient became extremely non-adherent, culture reverted at month 4 and he refused further treatment after 6 months. The remaining 18 patients were included in the analysis of the bacteriological effect of either strengthening a gatifloxacin-based STR with linezolid or replacing the fluoroquinolone with bedaquiline.

Of 18 patients, 5 were previously unsuccessfully treated with a STR. All five were treated with the BDQ-STR. The vast majority of patients had a high bacillary load on smear microscopy. Of 17 with fluoroquinolone-resistant RR-TB, MIC data showed high-level resistance in 16 patients. One patient treated with the LZD/GFX-STR had low-level fluoroquinolone resistance.

Of seven patients treated with a LZD/GFX-STR, three (43%) were cured relapse-free. No patient had stable culture conversion from month 1, and 2 (29%) at month 2. Three patients experienced treatment failure. Another patient died after two months of treatment while culture and smears

were still positive. This young woman started treatment in a very critical condition, with cavitary disease, a very high bacillary load and BMI of 11.6 kg/m2, with severe vomiting.

Of 11 patients treated with a BDQ-STR, nine (82%) were cured relapse-free. Of 11, seven (64%) converted at month 1 and 9 (82%) at month 2. One patient first had culture conversion at month 3 and was cured, but experienced relapse five months after cure. A second patient first converted on smear microscopy at month two but then died before culture could be done. The cause of death was recorded as cardiorespiratory insufficiency. Both patients had advanced TB disease, with a very low BMI, respectively 12.2 and 12.8, a high bacillary load, and converted relatively late.

Stable conversion occurred more rapidly in patients treated with a BDQ-STR (log-rank test: p=0.02; time to conversion was the time between treatment start and the first negative culture that was not followed by a positive culture -in one patient without culture results fluorescein diacetate vital staining [10] results were used). Stable culture conversion at 1 month occurred in seven of 11 patients on a BDQ-STR and in none of seven on a LZD/GFX-STR (p=0.01). Relapse-free cure (versus failure, relapse, or death) was more frequent in patients treated with the BDQ-STR (82% (9/11) vs 43% (3/7), p=0.09, Chi-squared test), but the difference was not significant at level 0.05.

Our study confirmed that bedaquiline can act as core drug for the treatment of patients with fluoroquinolone-resistant RR-TB.

Previous use is being included as a criterium to evaluate the likely effectiveness of TB drugs [7]. Our results suggest this mainly holds for the drug exerting the highest killing activity, the core drug of the regimen. Indeed, in our study the same background regimen was effective when combined with another core drug. “Previously used” should not be considered an absolute criterium for excluding a companion drug with lower killing activity than other drugs in the regimen.

In the one patient with relapse no resistance to BDQ was acquired on genotypic DST. Companion drugs are key to assure early resistance prevention. A study from Pakistan showed that second-line injectable drugs protected well against acquired bedaquiline resistance.[11] Bedaquiline-containing

regimens without high resistance preventing activity result in a too high rate of acquired bedaquiline resistance.[12]

In the LZD/GFX STR, gatifloxacin combined with linezolid during the early stage of treatment did not exert the same effect as bedaquiline in the GFX-STR. Despite the bactericidal activity of kanamycin in all patients treated with the LZD/GFX-STR and ethionamide in most, and the additional activity of linezolid, no patient on LZD/GX-STR had early stable conversion at one month, while the majority on the BDQ-STR experienced early conversion. Probably there was little residual activity of gatifloxacin and linezolid does not seem to drive early culture conversion, which suggests that linezolid does not qualify as core drug. Without core drug regimens are little effective.[8] On the other hand, in Niger linezolid was effectively used as companion drug in patients with fluoroquinolone-susceptible RR-TB and a contraindication for treatment with second-line injectable drugs [13]

Our sample size was too small to conclude whether relapse-free cure was significantly higher with 95% certainty for the BDQ-STR compared to the LZD/GFX-STR. However, data on culture conversion showed that the BDQ-STR had an earlier killing effect than the LZD/GFX-STR in a cohort mainly consisting of patients with fluoroquinolone-resistant cohort.

In conclusion, bedaquiline acted as core drug in a third-line RR-TB treatment regimen in patients with presumptive fluoroquinolone resistance, including patients previously treated with second-line drugs. A second-line injectable drug provided the necessary high resistance preventing activity.

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Conflicts of interest: B.C. de Jong reports grant funding from USAID for the STREAM trial on Bedaquiline for MDR-TB; and membership of a Panacea scientific advisort board, both within the 36 months prior to manuscript submission. All other authors declare no conflicts of interest.

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Authors' contributions: TD and AVD conceived the study. AVD, KJMA, MAH and MG collected and prepared the Damien Foundation Bangladesh data. MAH and MG conducted drug susceptibility testing. TD and AVD analysed the data. All co-authors contributed to the interpretation of the findings. AVD and TD wrote the first draft. All co-authors critically revised the subsequent versions and also approved the final version.

Ethics approval: The study protocol was approved by the Institutional Review Board of the ITM (1233/88), Antwerp, Belgium.

Data sharing statement: The data used for the analysis are shown in the table.

Table. Characteristics and outcomes of patients treated with a bedaquiline-based or linezolid-strengthened shorter rifampicin-resistant tuberculosis treatment regimen

Cohort/ patient	Baseline BMI (kg)	Baseline SSM AR; FDA	Previous unsuccessful SL regimen	Previous SL outcome	FQ pDST (gDST)	KM pDST	PTH pDST	Culture follow-up	Conversion	Outcome
BDQ-STR N or median (IQR)	17.8 (15.0-18.8)		Yes: 5 No: 6	FL: 4 RL: 1 NA: 6	R: 10 S: 1	S: 11	R: 1 S: 7 U: 3	Stable conversion: M1: 7 M2: 2 (incl 1 death) M6: 1 None: 1 (1 RL)		RL-free cure:9 RL: 1 Died: 1
A	18.8 (50)	3+; 2+	No *	NA	R GFXMIC 4 (94Gly)	S	S	N/NNNN_N_NN/NNNN (a)	M1	RL-free cure
B	16.7 (35)	3+; 2+	Yes (GFX-STR)	FL	R GFXMIC 8 (94Gly)	S	S	N/NNN_NN___/ (a)	M1	RL-free cure
C	21.6 (46)	3+; 1+	Yes (GFX-STR) *	FL	R GFXMIC 2 (94Tyr)	S	S	P/NNNNNN_NN/NNN	M1	RL-free cure
D	18.2 (52)	3+; 2+	Yes (LFX-STR)	FL	R GFXMIC 2 (94Tyr)	S	S	P/NPPP_N_NN/NNNN	M6	RL-free cure
E	15.4 (40)	2+; 2+	No	NA	R GFXMIC >2	S	U	P/PNNNN_N_N_N/NNNN	M2	RL-free cure
F	19.0 (48)	1+; Sc	No	NA	S	S	U	P/NNNN_N_NN/N	M1	RL-free cure
H	18.6 (50)	3+; 2+	Yes (OFX-reg)	RL	R GFXMIC >2	S	S	P/NNNN_N_NN/NNNN	M1	RL-free cure
I	15.0 (36)	3+; 3+	No	NA	R GFXMIC >2	S	U	P/NNNN_N_NN/N	M1	RL-free cure
J	17.8 (38)	3+; 2+	No *	NA	R GFXMIC >2	S	R	P/NNNN_N_NN/NNNN	M1	RL-free cure
K	12.2 (32)	3+; 2+	Yes (LFX-STR)	FL	R GFXMIC >2	S	S	P/PPNNNN_NN/P	M3/RL	Relapse
L	12.8 (30)	2+; 1+	No	NA	R GFXMIC >2	S	U	P/__ (b)	M2 (b)	Died
M	17.8 (38)	2+; 1+	No *	NA	R GFXMIC >2	S	R	P/NNNP	M1/STOP	STOP/LTFU

LZD/GFX-STR N or median (IQR)	16.9 (15.2-19.6)		Yes: 0 No: 7	NA:7	R:7	S: 7	R: 1 S: 7	M2: 2 M3: 1 None: 4 (3 FL, 1 died)		RL-free cure:3 FL: 3 Died: 1
p-value #	0.8 (0.7)	1.0; 0.7	0.04	NA	1.0	1.0	0.9	0.01		0.09 £
N	16.9 (46)	2+; 1+	No	NA	R GFXMIC 4 (94Gly)	S	S	P/PNNNN_N_NN/N_NN	M2	RL-free cure
O	15.2 (40)	3+; 3+	No	NA	R GFXMIC 2 (90Val)	S	S	P/PNN_N_N_NN/NNNN	M2	RL-free cure
P	19.2 (48)	3+; 2+	No	NA	R GFXMIC 1 (WT)	S	S	P/PPNNN_N_NN/NNNN	M3	RL-free cure
Q	16.6 (44)	1+; Sc	No	NA	R GFXMIC 8 (94Asn)	S	R	P/NNN_NN_PP	M1/FL	Failure
R	19.7 (45)	3+; 3+	No	NA	R GFXMIC 4 (91Pro)	S	S	P/PNNNN_N_NP	M2/FL	Failure
S	19.6 (52)	3+; 2+	No	NA	R GFXMIC 8 (94Gly)	S	S	P/PNNN_P_PP	M2/FL	Failure
T	11.6 (25)	3+; 2+	No	NA	R GFXMIC 2 (94Gly)	S	S	P/PP	No conv	Died
U	15.0 (38)	3+; 3+	No	NA	S	S	R	P/NNNN_N_N_N_/N_N	M1	RL-free cure
V	15.6 (42)	3+; 3+	No	NA	S	S	R	P/NNNN_N_NN__/NNNN	M1	RL-free cure

Drugs: B or BDQ = bedaquiline, C=clofazimine, E=ethambutol, Et=ethionamide, G or GFX =gatifloxacin, Hh=high-dose isoniazid, L=linezolid, L or LFX=levofloxacin, K or KM =kanamycin, O or OFX=ofloxacin, Pt or PTH=prothionamide, Z=pyrazinamide

BDQ-STR: bedaquiline-based shorter treatment regimen (4BKPtHhCEZ/ 5BCEZ)

LZD/GFX-STR: linezolid-based shorter treatment regimen (2LGKPtHhCEZ/ 2GKPtHhCEZ/ 5GCEZ)

OFX-regimen: 4OKPtHCEZ/ 12OHCEZ; GFX-STR: 4GKPtHCEZ/ 5GCEZ; LFX-STR: 4LfKPtHCEZ/ 5LfCEZ

Cat1=6-month rifampicin-based first-line regimen, Cat2: 8-month streptomycin-strengthened/rifampicin-based first-line regimen, MDR: second-line fluoroquinolone-based shorter treatment regimen

AR= auramine, BMI= body mass index, FDA= fluorescein diacetate vital staining, FL= failure, gDST=genotypic drug susceptibility testing, IQR=interquartile range, LTFU= lost to follow-up, N=number, NA= not applicable, pDST=phenotypic drug susceptibility testing, RL= relapse, SL= second-line TB treatment regimen, SSM= sputum-smear microscopy

R=resistant, S=susceptible, U=unknown; P=positive, N=negative, Sc=scanty; _=unknown

* Switched during the first or second month of fluoroquinolone-based RR-TB treatment to the BDQ-STR (in one patient during a second STR, after treatment failure for a previous second-line treatment outcome)

$: Culture results are shown as follows: baseline result / results during 9-11 months of treatment/ post-treatment results with 6-monthly sampling. In case no sputum sample was obtained, patients were assessed clinically.

Chi-squared test or Fisher's exact test for categorical variables, to assess correlations between categorical variables and belonging to the BDQ-STR or LZD/GFX-cohort, not including the 3 patients excluded. Also observations with missing data were excluded. Kruskal-Wallis rank test for the continuous variable BMI.

£: Binary variable for outcome: relapse-free cure as favorable and failure, relapse or death as unfavorable outcome

&: no bedaquiline acquired resistance on genotypic DST

(a) both cases: at baseline sputum smear microscopy positive on auramine (AR) and fluoresceine diacetate (FDA) vital staining (thus showing viability), then conversion at M1; (b) conversion on AR and FDA at month 2

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