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Randomized Pilot Trial of Eight Weeks of Bedaquiline (TMC207) Treatment for Multidrug-Resistant Tuberculosis: Long-Term Outcome, Tolerability, and Effect on Emergence of Drug Resistance

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The 2-year follow-up results for a randomized placebo-controlled study of 47 patients with multidrug-resistant pulmonary tuberculosis treated with either the new diarylquinoline TMC207, recently renamed bedaquiline, or placebo, added to the first 8 weeks of a background regimen, are presented. Bedaquiline significantly reduced the time to culture conversion over 24 weeks (hazard ratio, 2.253; 95% confidence interval, 1.08 to 4.71; $P = 0.031$). With the exception of nausea reported in 26% of patients receiving bedaquiline and none receiving placebo, adverse events occurred at similar frequencies in both groups of patients: bilateral hearing impairment, extremity pain, acne, and noncardiac chest pain occurred in 13 and 21%, 17 and 13%, 9 and 17%, and 4 and 17% of patients, respectively, receiving bedaquiline or placebo. Excluding resistance to ethambutol and ethionamide, only one patient receiving bedaquiline acquired resistance to companion drugs, but five patients receiving placebo (4.8% versus 21.7%; $P = 0.18$) acquired resistance to companion drugs, and resistance to ofloxacin was acquired in four patients receiving placebo and none receiving bedaquiline (0% versus 22%; $0 = 0.066$). In all, 23 patients (49%), including 13 receiving placebo (54%) and 10 receiving bedaquiline (44%), discontinued the study prior to its completion, 12 during the first 24 weeks of treatment. Eight subjects were withdrawn for noncompliance or default, and seven withdrew consent, citing the rigorous program of investigations for safety and pharmacokinetic monitoring. Bedaquiline may contribute to the management of multidrug-resistant tuberculosis by effecting more rapid sputum culture negativity and by preventing acquired resistance to companion drugs.

Multidrug-resistant (MDR) tuberculosis (TB) is a serious form of TB and the term MDR implies resistance to at least the essential first-line agents isoniazid (INH) and rifampin (RMP); because INH and RMP are no longer effective, patients with MDR pulmonary TB must be treated for at least 20 months with potentially toxic, less efficacious drugs (20). MDR *Mycobacterium tuberculosis* isolates will frequently also be resistant to the other first-line drugs pyrazinamide (PZA), ethambutol (EMB), or streptomycin (or SM) and, at times, other drugs such as ethionamide (Eth), a fluoroquinolone, or injectable drugs such as kanamycin (KAN), amikacin, or capreomycin (CAP). MDR TB with additional resistance to the last two mentioned classes is termed extensively drug-resistant (XDR). The spread of MDR TB, particularly among communities with a high prevalence of human immunodeficiency virus (HIV) infection, is threatening the foundations of TB control programs worldwide (19). TMC207, recently renamed bedaquiline, is a diarylquinoline with a novel mode of action specifically inhibiting mycobacterial ATP synthase (1).

The present randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of bedaquiline when it is added to a background regimen (BR) in newly diagnosed patients with MDR pulmonary TB was conducted in two stages. In the first stage, bedaquiline was added to the BR for 8 weeks. After a planned break in recruitment to confirm that anticipated serum drug levels were reached, the trial moved to the second stage, where bedaquiline was added to the BR for 24 weeks in a new group of patients. The 8-week results of the first stage (8 weeks of bedaquiline) were reported previously. Of 21 evaluable subjects receiving bedaquiline in addition to BR, 10 (47.6%) were sputum culture negative after 8 weeks compared to only 2 of 23 (8.7%) receiving placebo in addition to BR ($P = 0.003$) (5). We describe the 2-year outcome and the difficulties and complications encountered during follow-up of this first trial stage.

MATERIALS AND METHODS

Study population. The study subjects were newly diagnosed with MDR pulmonary TB due to *M. tuberculosis* resistant to (at least) both INH and RMP, who had either not been treated or had received only the first-line drugs INH, RMP, EMB, PZA, or SM. Participating centers were located all in South Africa. The full details on the inclusion and exclusion criteria, the details of treatment, and the results at 8 weeks have been presented previously (5). Briefly, the patients had a median age of 33 years (range, 18 to 57 years) and a median weight of 50.7 kg (range, 36 to 83 kg); 75% were male, and 85% had cavitary pulmonary disease. The BR consisted of standard MDR drugs used in South Africa with few exceptions. In all 47 patients it comprised Eth and KAN; all but 1 (2.1%) patient received ofloxacin (OFL), 29 received (61.7%) EMB, 28 received (59.6%) terizidone (TER)-cycloserine (CS), 2 (4.3%) patients received dapsone, and single patients received CAP, clarithromycin, erythromycin, and INH (at 10 mg/kg) and *para*-aminosalicylic acid. Substitutions within classes were permissible in the case of a shortage of drug supply, intolerance, or when drug susceptibility results became available. Moxifloxacin, levofloxacin, and gatifloxacin were not available to the Tuberculosis Control Programme in South Africa at the time of the study.

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Microbiological assessments. Spot sputum samples to assess the presence or absence of *M. tuberculosis* by qualitative culture in liquid medium (MGIT 960; Becton Dickinson, Sparks, MD) and by sputum smears to detect acid-fast bacilli on microscopy were collected at baseline and at every visit (weekly up to week 8 and then at weeks 10, 12, 16, 24, 36, 48, 60, 72, 84, and 104). Susceptibility testing was performed centrally (Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium) on spot sputum samples collected at baseline, at weeks 8, 24, 60, and 72, and shipped in cetyl-pyridinium chloride at room temperature. Additional drug susceptibility assessments were made in case of failure to respond to treatment or if a new positive culture was recorded after culture conversion. Susceptibility to first-line drugs and those included in the background regimen was determined by the proportion method (3, 9). Bedaquiline MICs were measured using a resazurin microtiter assay (REMA) (13).

Clinical safety and pharmacokinetic assessments. Assessment of vital signs, physical examination, laboratory profiling, electrocardiography, and chest radiography were performed at regular intervals. Adverse events were graded according to the Division of Microbiology and Infectious Diseases adult toxicity tables. All subjects were monitored for 104 weeks unless they discontinued prematurely, which was due either to the withdrawal of consent or as a result of investigator concerns regarding safety and/or collaboration with essential study procedures. Sampling for the determination of plasma concentrations of bedaquiline and its metabolite M2 occurred weekly up to week 8 and then at weeks 10, 12, 16, 24, 36, 48, 60, 72, 84, and 104. The M2 metabolite has activity against *M. tuberculosis* that is 4 to 5 times lower than that of bedaquiline itself.

Statistical evaluation. The efficacy variable for the final stage I analysis was the time to sputum culture conversion during the first 24 weeks postrandomization, which was defined as the time from the initiation of treatment to the first of two negative cultures collected at least 25 days apart with no confirmed positive intermediate cultures. A cutoff at 25 days was chosen since monthly visits were scheduled to be 28 ± 2 days apart. Subjects were not evaluable for the primary endpoint when found to be culture negative at baseline or when they were found to have XDR TB at randomization. Subjects dropping out during the 24-week treatment period were considered treatment failures irrespective of culture status at dropout and were censored at week 24. Subjects whose sputum culture had reverted from negative to positive were again considered culture positive. For comparison of treatment groups, a Cox proportional model was used with the degree of radiological lung cavitation at baseline and the pooled trial center as covariates. A secondary efficacy variable was the proportion of sputum culture conversion at different time points.

RESULTS

Subjects. Twenty-three and twenty-four subjects received bedaquiline or placebo, respectively. Table 1 summarizes details of the 47 patients randomized and treated with regard to baseline drug resistance, HIV status, chest radiography findings, the attainment of culture negativity, and the emergence of resistance. Noncavitating disease was present in only three patients in the bedaquiline group and four in the placebo group; disease was bilateral in six (26.1%) patients in the bedaquiline group and seven (29.2%) in the placebo group. Only three patients in each group were HIV infected. Figure 1 shows the disposition of patients. One subject in each group was discontinued in the second week on the study and excluded from the efficacy analysis because a result of XDR TB on a sputum sample prior to enrollment became available. One additional subject in the bedaquiline group was excluded from the efficacy analysis because the baseline culture remained negative, but the subject completed follow-up. Forty-four patients were included in the efficacy analysis, whereas all 47 randomized and treated patients were in included in the safety analysis. In total, 23 (48.9%) patients discontinued during the course of the study: 13 in the placebo group and 10 in the bedaquiline group. Twelve subjects discontinued during the first 24 weeks, and a further 11 discontinued before completion of follow-up after 104 weeks. In addition to the two subjects with XRD TB in the first 2 weeks, the investigators also withdrew eight subjects for noncompliance or treatment default. Two subjects in the placebo group were withdrawn at week 63 because of increasing levels of drug resistance. Seven subjects withdrew consent, citing as the reason the intensity and frequency of visits for safety monitoring procedures and pharmacokinetic sampling. Three subjects were transferred out and were lost to follow-up upon changing their address, and one patient in the bedaquiline group died. There were no relevant differences between randomization groups with respect to any demographic parameters, baseline disease characteristics, baseline resistance profile, and the reasons for, or the timing of, discontinuation.

Microbiological outcome. Microbiological outcomes were assessed after the first 24 weeks and at end of the trial at 104 weeks (Table 1). Figure 2A shows culture conversion over 24 weeks, with all subjects who discontinued during the first 24 weeks carried forward as not converting, irrespective of their microbiological status at the time of discontinuation. The efficacy difference was statistically significant (hazard ratio, 2.253; 95% confidence interval [CI], 1.08 to 4.71; $P = 0.031$). The times to 50% culture conversion were 78 days in the bedaquiline group and 129 days in the placebo group. At week 24, 81.0% of the subjects in the bedaquiline group and 65.2% of the subjects in the placebo group had submitted sputum for an MGIT culture that remained negative. In the bedaquiline group, all four subjects scored as treatment failures had discontinued before week 24 and thus did not submit sputum; two (50%) of these were culture negative at discontinuation. In the placebo group, six of the eight subjects scored as treatment failures had discontinued prior to week 24, but only one of these (12.5%) was sputum culture negative at dropout. Figure 2B shows the culture conversion over 24 weeks with subjects who discontinued, scored according to their culture status at discontinuation and kept in the analysis. With this method, the efficacy difference was larger (hazard ratio, 3.135; 95% CI, 1.51 to 6.53; $P = 0.002$), the time to 50% culture conversion was shorter (68 days in the bedaquiline group and 126 days in the placebo group), and more subjects were scored as culture converted (90.5% in the bedaquiline group and 69.6% in the placebo group). After 104 weeks, treatment success was achieved in 11 patients (52.4%) in the bedaquiline group and 11 patients (47.8%) in the placebo group. In the bedaquiline group, treatment failure was scored in 10 subjects (47.6%); of these, two subjects withdrew with positive cultures before week 24, one subject was found to be culture positive on completion, one subject withdrew with a positive culture at week 92 that had become negative before, and 6 subjects were culture negative at discontinuation. All 12 subjects scored as failures in the placebo group had discontinued, and 10 of these were culture positive at discontinuation. This group included three subjects who were culture negative at week 24 but became positive again before discontinuation.

Drug resistance. Drug susceptibility data are summarized in Table 1. Baseline resistance data were available for 18 subjects in the bedaquiline group and 21 subjects in the placebo group. Noteworthy were the high rates of resistance to the remaining "first-line" agents, EMB (66.7%), PZA (66.7%), and SM (79.5%) but with lower rates of resistance to OFL (13%), KAN (13%), and CAP

TABLE 1 HIV status, chest radiography findings, drug resistance, and culture status at baseline, 8 weeks, 24 weeks and 104 weeks[a]

	Baseline				8 wk		24 wk		104 wk	
Treatment group and patient	HIV	CXR	Drug resistance profile	Bedaquiline MIC (μg/ml)	Culture status	Acquired resistance	Culture status	Acquired resistance	Culture status	Acquired resistance
Bedaquiline + BR group										
1	P	UC	HR	0.06	C–		C–		–/Dis 24w	
2	N	UC	HRS	0.03	C+	NG	C–		C–/Com	
3	N	UC	HRZ	0.03	C–		C–		C–/Com	
4	N	UC	HRSE	0.008	C–		–/Dis 17w		–/Dis 17w	
5	N	UC	HRSE	0.03	C–		C–		C–/Com	
6	N	NC	HRZS	0.01	C–		C–		C+/Com	
7	N	NC	HRZS	0.008	–/Dis 3w		–/Dis 3w		–/Dis 3w	
8	N	BC	HRSE	0.03	C–		C–		–/Dis 36w	
9	P	UC	HRSE	0.06	C+	NG	C–		C–/Com	
10	N	UC	HRZSE	0.06	C–		C–		–/Dis 26w	
11	N	UC	HRZSE	0.06	C+	NG	C–		C–/Com	
12	N	BC	HRSE	0.01	C–		C–		C–/Com	
13	P	BC	HRZSEEth	0.25	C–		C–		C–/Com	
14	N	UC	HRZSE	0.25	–		–/Dis 2w		–/Dis 2w	
15	N	UC	HRSEOZ	0.01	C–		C–		C–/Com	
16	N	BC	HRZSEEth	0.03	C+	K, C	C–		C+/Com	
17	N	BC	HRZSEK	0.06	C–		C–		–/Dis 93w	
18	N	UC	NG	NG	C+	NS	C–		–/Dis 41w	
19	N	NC	NG	0.03	C+ at 7w	NG	C–		C–/Com	
20	N	UC	NG	0.01	C+	NS	C–		C–/Com	
21	N	BC	NG	NG	C–		–/Dis 14w		–/Dis 14w	
22*	N	UC	HRZSEOKC	0.01	–/Dis 2w		–/Dis 2w		–/Dis 2w	
23**	N	UC	NG	NG	C–		C–		C–/Com	
Placebo + BR group										
1	N	UC	HR	0.01	C–		–/Dis 10w		–/Dis 10w	
2	N	UC	HR	0.03	C–		C–		C–/Com	
3	P	UC	HR	0.24	C+	No	C–		C–/Com	
4	N	UC	HRES	0.03	C+	Z, E reverted	C–		C–/Com	
5	N	BC	HRS	0.01	C–		C–		C–/Com	
6	N	UC	HRZ	0.03	C+	NS	–/Dis 16w		–/Dis 16w	
7	N	UC	HRES	0.008	C–		–/Dis 16w		–/Dis 16w	
8	N	BC	HRZS	0.008	C+	E	C+	E, O	–/Dis 49w	
9	N	NC	HRZE	0.01	C+	E reverted	C–		–/Dis 63w	C+ at 60w: O, S
10	N	UC	HRZK	0.06	C+	O, E, S	C+	NG	–/Dis 63w	
11	N	BC	HRZS	0.01	C+	NG	C–		–/Dis 47w	
12	N	UC	HRZSE	0.12	C+	O	C–		C–/Com	
13	N	BC	HRZSE	0.03	C+	NS	C–		C–/Com	
14	N	UC	HRZSE	0.06	C+	No	–/Dis 11w		–/Dis 11w	
15	N	UC	HRZSE	0.06	C+	No	C–		C–/Com	
16	P	UC	HRZSE	0.01	C+	NG	C–		C–/Com	
17	N	UC	HRZSE	0.06	C–		C–		–/Dis 33w	
18	N	BC	HRZSEO	0.06	C+	NG	C–		–/Dis 41w	
19	N	BC	HRZSEO	0.12	–/Dis 5w		–/Dis 5w		–/Dis 5w	
20	P	NC	HRZSEKEthC	0.25	C+	NG	C–		C–/Com	C+ at 60w: Eth reverted
21	N	BC	NG	0.03	C+	NG	C–		C–/Com	
22	N	UC	NG	0.01	C–		–/Dis 18w		–/Dis 18w	
23	N	NC	NG	NG	C–		C–		C–/Com	
24*	N	NC	HRZSEOKEthC	0.03	–/Dis 2w		–/Dis 2w		–/Dis 2w	

[a] BR, background regimen; Com, completed; Dis, discontinued; N, negative; NG or NS, no growth or no sample; P, positive; w, week. Chest radiography: BC, bilateral cavitary disease; CXR, chest radiograph; NC, noncavitary disease (no cavity = ≤2-cm diameter); UC, unilateral cavitary disease. Drugs: C, capreomycin; E, ethambutol; Eth, ethionamide; H, isoniazid; K, kanamycin; O, ofloxacin; R, rifampin; S, streptomycin; Z, pyrazinamide. Drug susceptibility tests were performed using the agar proportion method for the background regimen. TMC207 MIC, MIC obtained with a resazurin microtiter assay. *, Subjects withdrawn at 2 weeks because of XDR TB diagnosed from sputum submitted prior to enrollment; **, subject not included in efficacy population because of negative baseline culture.

(8%). In the bedaquiline group, one subject additionally resistant to Eth, EMB, SM, and PZA but sensitive to bedaquiline, CAP, KAN, and OFL at baseline acquired resistance to KAN and CAP at week 8. At weeks 24, 60, and 72 posttreatment, the MGIT cultures for this subject were negative, and no drug susceptibility testing could be performed. In the placebo group, eight subjects had data both at baseline and at week 8. Isolates from two subjects developed resistance to OFL, from one subject to PZA, from two subjects to EMB, and from one subject to SM, while isolates from two subjects were determined to be susceptible to EMB after previously being recorded as resistant. At week 24, drug susceptibility data were available for only one subject who had already been found to be resistant to EMB at week 8 and was now found additionally resistant to OFL. Of the two subjects with data at week 60, one subject had developed resistance to OFL and SM, and the other subject, resistant to HRZSEKEth and C (see resistance profiles in Table 1) at baseline, was culture negative at weeks 8 and 24 but became culture positive again at week 60. At this point, it was reported that the subject was now sensitive to Eth. Upon assessment at the end of the trial, this subject was again culture negative. In total, therefore, 4/18 subjects with initially documented OFX susceptibility receiving placebo (22.2%) and 0/16 receiving bedaquiline acquired resistance to OFL during treatment (Fisher exact test, $P = 0.066$).

For bedaquiline, 70% of the 43 baseline isolates had a bedaquiline MIC of ≤0.03 μg/ml and 95% had a bedaquiline MIC of ≤0.12 μg/ml (range, 0.003 to 0.240 μg/ml). Postbaseline MICs

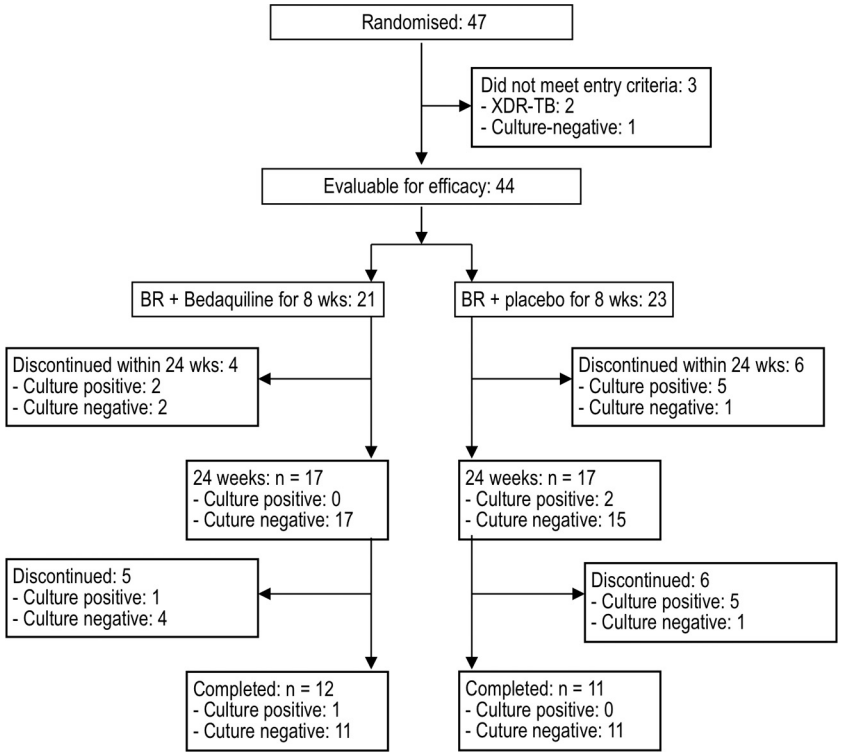

FIG 1 Patient disposition and culture status. All 47 randomized patients were analyzed for safety. For the efficacy analysis, 44 patients were available: 2 subjects (one in each group) were diagnosed with XDR TB on a sputum sample submitted before enrollment and were withdrawn within 2 weeks of randomization, and 1 subject in the bedaquiline group remained culture negative at baseline.

could be obtained from a few patients, but no significant differences compared to baseline MICs were observed.

Adverse events. One subject in the bedaquiline group died from an autopsy-confirmed myocardial infarction that was considered unrelated to study medication. Most remaining adverse events registered during the phase following the 8 weeks of study medication (5) were mild or moderate and similar to those known to occur in patients receiving second-line antituberculosis chemotherapy. The most commonly reported events were nausea (26.1% of subjects in the bedaquiline group and none in the placebo group), bilateral hearing impairment (13.0 and 20.8%, respectively), viral infection (0 and 20.8%, respectively), extremity pain (17.4 and 12.5%, respectively), acne (8.7 and 17%, respectively), and noncardiac chest pain (4.3 and 16.7%, respectively). Except for nausea, which was more common in the bedaquiline group, the incidence of these events was not statistically different between groups.

No consistent or clinically relevant changes in heart rate or electrocardiographic QRS or PR interval were observed during the 8 weeks of bedaquiline dosing (5) or thereafter. Increases in the mean QT interval corrected using Fridericia's formula (QTcF) were observed in both treatment groups over the entire study duration and were more pronounced in the bedaquiline treatment group. None of the absolute values for QTcF were greater than 500 ms, and no adverse events were associated with electrocardiographic changes.

Elimination of bedaquiline and M2. The treatment pharmacokinetics of bedaquiline and M2 for up to 8 weeks have been described previously (5). After 8 weeks of bedaquiline administration, the mean terminal elimination half-life was similar for bedaquiline (164 days; range, 62 to 408 days) days and its metabolite M2 (159 days; range, 69 to 407 days). At study end, 96 weeks after the last dose, the bedaquiline and M2 plasma concentrations were still quantifiable in all but one and three subjects, respectively, with a median concentration of 10.0 ng/ml (range, 2.24 to 43.6 ng/ml) and 2.58 ng/ml (range, 1.64 to 11.6 ng/ml), respectively.

DISCUSSION

This rigorously conducted placebo-controlled, double-blind, randomized trial has demonstrated the antimycobacterial activity, safety, and tolerability of bedaquiline in patients with MDR pulmonary TB. Patients receiving bedaquiline in addition to a BR during the initial 8 weeks of MDR treatment reached sputum culture negativity in the MGIT system significantly more quickly than patients receiving placebo and were at lower risk of acquisition of additional drug resistance over the whole duration of follow-up.

The statistical approach assessing the main outcome of culture conversion used in the present study differs slightly from that in the previous publication (5) and accords with the method that will be followed with 24-week bedaquiline dosing in the second stage of this study. Only subjects who experience sputum culture conversion and submit a confirmed negative sample at 24 weeks are scored as converted (Fig. 2A), which is more stringent than scoring outcomes according to culture status irrespective of whether participants left the study before 24 weeks or not (Fig. 2B). Bedaquiline retained a statistically significant advantage with both approaches despite the fact that 50% of the discontinued subjects

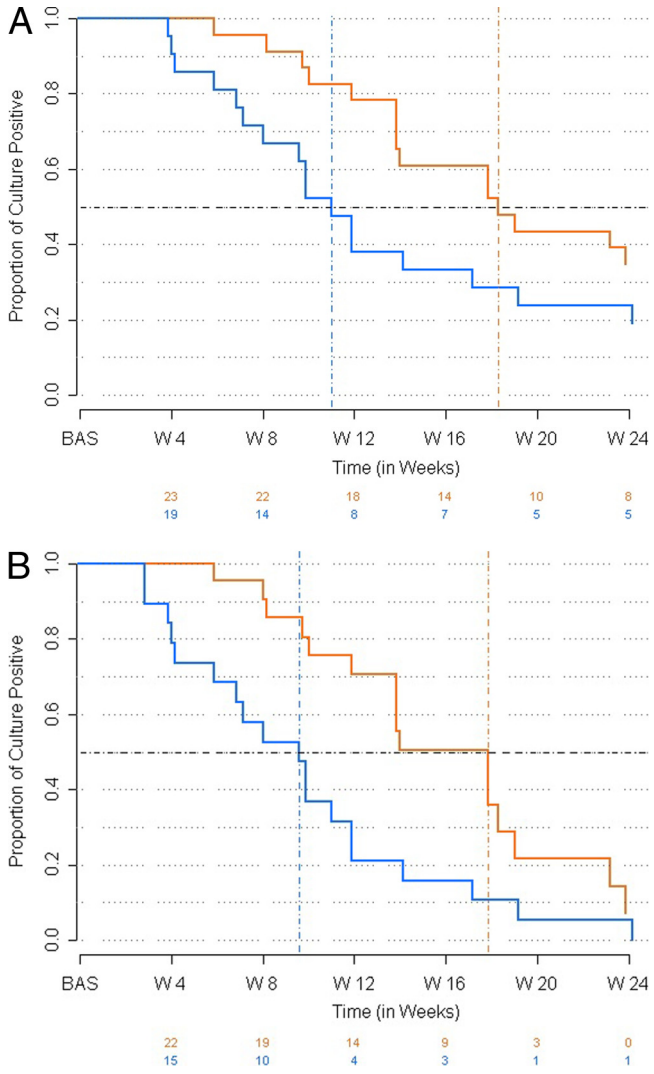

FIG 2 Proportion of patients with positive sputum cultures and time to conversion. (A) Culture conversion over 24 weeks among subjects who discontinued during the first 24 weeks carried forward as not converting (hazard ratio, 2.253; 95% CI, 1.08 to 4.71; $P = 0.031$). In the bedaquiline (orange line, above) and placebo (blue line, below) groups, the times to 50% culture conversion were 78 and 129 days, respectively, and 17/21 (81.0%) and 15/23 (65.2%) of the subjects, respectively, submitted negative sputum samples at week 24. (B) Culture conversion over 24 weeks among subjects who discontinued scored according to their culture status at the time of discontinuation and kept in the analysis (hazard ratio, 3.135; 95% CI, 1.51 to 6.53; $P = 0.002$). In the bedaquiline (orange line, above) and placebo (blue line, below) groups, the times to 50% culture conversion were 68 and 126 days, respectively, and 19/21 (90.5%) and 16/23 (69.6%) of the subjects, respectively, were culture negative at week 24 or at the time of discontinuation.

receiving bedaquiline had attained culture negativity before discontinuation compared to only 12.5% receiving placebo. A point can certainly be made in this context that long-term studies involving MDR TB patients should follow simple, flexible protocols and ensure strong support for adherence to treatment and participation in follow-up study assessments.

An important part of this trial was the thorough assessment of drug susceptibility of isolates obtained from the sputum of all of the enrolled patients before and during treatment. Even after acknowledging the difficulties with resistance testing of PZA (7), EMB (10), and Eth (16), the results summarized in Table 1 paint a very disturbing picture that emphasizes the potential weakness of commonly used standardized regimens for the treatment of MDR TB. The overall resistance at baseline to the remaining "first-line" agents EMB, PZA, and SM exceeded 66%; furthermore, 13% of the isolates were resistant to KAN and OFL. That this is a realistic picture is supported by other studies from the United States (4) and by molecular genetic studies of resistance among isolates from the Western Cape Province of South Africa (8, 11, 18).

The acquisition of additional resistance during the trial, mainly in the placebo group, especially in the form of OFL or KAN resistance leading to a pre-XDR resistance profile, despite documentation of directly observed therapy, is reason for grave concern. Additional resistance was acquired by 5 of 21 patients with available baseline sensitivity results (23.8%) in the placebo group, and in four cases this occurred, or commenced, during the first 8 weeks of treatment. In four patients (19%) this included developing resistance to OFL. In two subjects this was detected during the first 8 weeks of treatment and in one subject each during the periods 9 to 24 weeks and 25 to 104 weeks after commencing treatment. In the bedaquiline group, only one patient acquired resistance to KAN and CAP who had had baseline resistance to INH, RMP, PZA, SM, EMB, and Eth. Not surprisingly, although culture negative at 24 weeks, this patient became culture positive again upon completion of 104 weeks of therapy. It seems that even with good treatment adherence, the available second-line agents are often inadequate to protect each other from the development of resistance (2). No significant decrease in susceptibility to bedaquiline was observed in the bedaquiline treatment group.

Fewer resistance results were available in bedaquiline-treated subjects who not only achieved culture negativity more rapidly but also submitted a larger proportion of sputum samples that did not grow a culture for resistance testing (bedaquiline, 4/7 [57%]; placebo, 5/15 [33%]; Fisher exact test, $P = 0.097$). A likely explanation is a lower bacterial sputum load, which would further reduce the chance for the development of resistance. Despite the low number of observations, preventing these findings from reaching statistical significance, and despite lacking clinically detectable very early bactericidal activity (15), it is noteworthy that bedaquiline may protect against the acquisition of additional resistance and XDR TB in patients with MDR TB.

Although a large proportion of patients experienced adverse events during the period of BR treatment, the incidence was similar in the patients who received bedaquiline (82.6%) compared to those who had received placebo (79.2%). Other recent studies of MDR TB treatment in southern Africa have recorded a similarly high incidence of adverse events (17). The majority of the adverse events recorded here were of mild or moderate intensity. Nonetheless, the frequency of these events probably contributes significantly to the difficulties encountered in managing MDR TB. These were compounded in this trial by the reluctance of some patients to continue with the necessary arduous schedule of investigations and assessments required for the evaluation of a new agent.

The observed terminal elimination half-life of bedaquiline and M2 of ~5.5 months can likely be explained by slow release of bedaquiline and M2 from peripheral tissue compartments. Both bedaquiline and M2 accumulate in various tissues in preclinical species (12), which is likely a result of the cationic amphiphilic

characteristics of these compounds. Cationic amphiphilic drugs (CAD) may cause intracellular accumulation of phospholipids in association with drug accumulation (a finding indicative of phospholipidosis), as has been observed for bedaquiline and M2 preclinically, as well as for many marketed drugs (6, 12). Upon termination of drug intake, the phospholipidosis is reversible as the drug is eliminated from the tissues. The time course of reversal is dependent on the dissociation rate constant of the CAD from the phospholipid and the elimination rate of the CAD from the tissue, which may result in a prolonged elimination half-life (14).

Conclusion. The final results of the first stage of this randomized controlled study confirm the significant bactericidal activity of bedaquiline in patients treated for MDR TB. The addition of bedaquiline for 8 weeks was safe and associated with earlier culture negativity. The overall incidence of adverse events was high and reflects the poor tolerability of the second-line companion agents. The emergence of drug resistance was substantial and may have been reduced by the concurrent administration of bedaquiline. Further study of the emergence of resistance among patients being treated for MDR TB is needed.

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