Treatment Outcomes and Adverse Drug Effects of Ethambutol, Cycloserine, and Terizidone for the Treatment of Multidrug-Resistant Tuberculosis in South Africa

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ABSTRACT

Treatment outcomes among multidrug-resistant tuberculosis (MDR-TB) patients receiving ethambutol, cycloserine, or terizidone as part of a standardized regimen were compared, determining occurrence of serious adverse drug events (SADEs). Newly diagnosed adult MDR-TB patients were enrolled between 2000 and 2004, receiving a standardized multidrug regimen for 18 to 24 months, including ethambutol, cycloserine, or terizidone. Cycloserine and terizidone were recorded individually. SADEs and factors associated with culture conversion and unfavorable treatment outcomes (default, death, treatment failure) were determined. Of 858 patients, 435 (51%) received ethambutol, 278 (32%) received cycloserine, and 145 (17%) received terizidone. Demographic and baseline clinical data were comparable. Successful treatment occurred in 56%, significantly more in patients receiving cycloserine (60%) and terizidone (62%) than in those receiving ethambutol (52% [P = 0.03]). Defaults rates were 30% in ethambutol patients versus 15% and 11% for cycloserine and terizidone patients, respectively. Terizidone was associated with fewer unfavorable outcomes (adjusted odds ratio [AOR], 0.4; P = 0.008; 95% confidence interval [CI], 0.2 to 0.8). Patients receiving cycloserine were more likely to achieve culture conversion than those receiving ethambutol or terizidone (AOR, 2.2; P = 0.02; 95% CI, 1.12 to 4.38). Failure to convert increased the odds of unfavorable outcomes (AOR, 23.7; P < 0.001; 95% CI, 13 to 44). SADEs were reported in two patients receiving ethambutol, seven patients receiving cycloserine, and three receiving terizidone (P = 0.05). Ethambutol was associated with high culture conversion and default rates. Cycloserine achieved higher culture conversion rates than terizidone. Fewer patients on terizidone experienced SADEs, with lower default rates. The differences that we observed between cycloserine and terizidone require further elucidation.

KEYWORDS: Mycobacterium tuberculosis, adverse drug effects, cycloserine, ethambutol, multidrug resistance, terizidone, tuberculosis

INTRODUCTION

The global estimate for drug-resistant (DR) strains of tuberculosis (TB) was 558,000 cases, of which only an estimated 25% had been started on therapy in 2018 (1). Equally concerning is that it has been estimated that 3 in every 1,000 people globally are infected with latent multidrug-resistant

(MDR) TB, and this prevalence is more than doubled in children under 25 years of age (2). The older second-line drugs (SLDs) used for MDR-TB have much lower potency than the two mainstay first-line drugs (FLDs) used for susceptible TB, viz. isoniazid and rifampicin. Due to this limitation of SLDs, patients with MDR-TB, who are ineligible for the recently introduced shorter regimens with the new antituberculotics, must be treated with at least five drugs for a total treatment duration of 18 to 20 months, which may be modified according to the patient's response to therapy (3). SLDs are also considerably more toxic than FLDs, often resulting in treatment abandonment or withdrawal of the drug(s) due to occurrence of adverse drug events (ADEs) (3).

When MDR-TB emerged in the 1980s and 1990s, certain drugs developed during the 1950s and 1960s for treatment of TB received renewed interest in order to design a treatment regimen consisting of drugs that patients had not received previously. Among these drugs was cycloserine, which was developed in the 1950s. From the limited use of the two drugs in the previous century, it was known that cycloserine caused central nervous system disturbances of which many were deemed serious, but terizidone was associated with fewer ADEs (4–7). During this period, only two small studies reported on the comparative efficacy but not on ADEs (7, 8). Cycloserine is a cyclic monomer of alanine (9), which results in the drug's toxicity through the inhibition of pyridoxal phosphate (PLP; a vitamin B6 derivative) (10). PLP is a biocatalyst in the basic metabolism of both prokaryotes and higher eukaryotes (11). Terizidone (Terivalidin) is a dimer of cycloserine (12, 13). Production of cycloserine was stopped in the late 1990s, and ethambutol was included instead in MDR regimens despite its weak anti-TB activity and widespread resistance (14, 15). Once cycloserine and terizidone again became available in 2003, these were recommended as alternatives for ethambutol (16), while acknowledging that there was limited evidence for the comparative safety and efficacy between terizidone and cycloserine (3).

Cycloserine and terizidone are listed as category B drugs for inclusion in all long MDR-TB treatment regimens (3). Both drugs in this group lack information about their safety and efficacy, and further research has been advocated in this regard (3). However, cycloserine and terizidone are considered to be last options due to toxicity profiles; nevertheless, these are widely used (14, 17). An advantage of cycloserine and terizidone is that these compounds are neither cross-resistant with other TB drugs (18) nor have any known interaction with other TB drugs. Cycloserine and terizidone are often used interchangeably and not recorded as two separated drugs (19), which limits the understanding of whether the different molecular structures have an impact on the compounds' efficacy and safety. As more novel agents are becoming available for treatment of DR-TB and as TB has emerged as the major infectious contribution in global burden of disease studies (20), there is once again renewed interest in the potential of older drugs as companion drugs in the DR-TB regimens. These older drugs have the potential to prevent development of drug resistance against the new anti-TB drugs and to reduce the risk of relapse (21, 22).

South Africa started programmatic management of MDR-TB in 2000 under DOTS-Plus (DP) and used a standardized regimen of four drugs and ethambutol, terizidone, or cycloserine as the fifth drug (16). In DP, cycloserine and terizidone were recorded as two separate drugs. Among the 858 patients who were treated with the standardized regimen from 2000 to 2004, 145 patients received terizidone, 278 patients received cycloserine, and 435 patients received ethambutol. In an attempt to contribute to our limited understanding of the efficacy and safety of cycloserine and terizidone against ethambutol independently, we compared the treatment outcomes and occurrence of serious adverse drug effects (SADEs) among a large national cohort of patients treated under routine conditions at multiple sites. We defined an unfavorable outcome as failure to culture convert to

negative, loss to follow-up, or death. We stratified this historic cohort by which of the three drugs anti-TB agents they received in their regimen and analyzed differences among the three drugs.

RESULTS

Patient population

A total of 1,737 new MDR-TB cases were enrolled for DP, among which 858 (49.4%) patients received standardized treatment. Patients were excluded from the analysis if they had tuberculosis with unknown ethambutol resistance, with known ethambutol resistance but received ethambutol, or if they had received ethambutol, cycloserine, and terizidone interchangeably (Fig. 1). The cohort consisted of 435 (50.7%) patients receiving ethambutol, 278 (32.4%) receiving cycloserine, and 145 (16.9%) receiving terizidone (Table 1). Patients among these three groups were very similar at baseline in gender, age, HIV status, previous TB, weight, and culture status (Table 1). The mean age of the cohort was 36.3 years (18 to 73 years), was mostly male (546 [63.7%]), and among the 553 (64.4%) who knew their HIV-status, 208 (37.6%) were HIV infected (Table 1). Baseline chest X-ray (CXR) information was available for 568 (66.2%) patients: the majority (482 [84.9%]) had bilateral pulmonary disease. Of those presenting with bilateral disease, 220 (45.6%) received ethambutol, 174 (36.1%) received cycloserine, and 88 (18.3%) received terizidone. Certain centers had very low patient enrolments in the study; thus, not all drugs may have been included in the randomized treatment protocols at those centers. The mean weight of the patients at baseline was 51.5 kg (standard deviation [SD], ±10.6; range, 24 to 104 kg), and 90.1% (682/757) weighed less than 65 kg, among which a further 325 (47.7%) weighed less than 50 kg. Most patients gained weight during the first 4 months of treatment, but 27.1% had not gained any weight (experienced weight loss), although this was not significant.

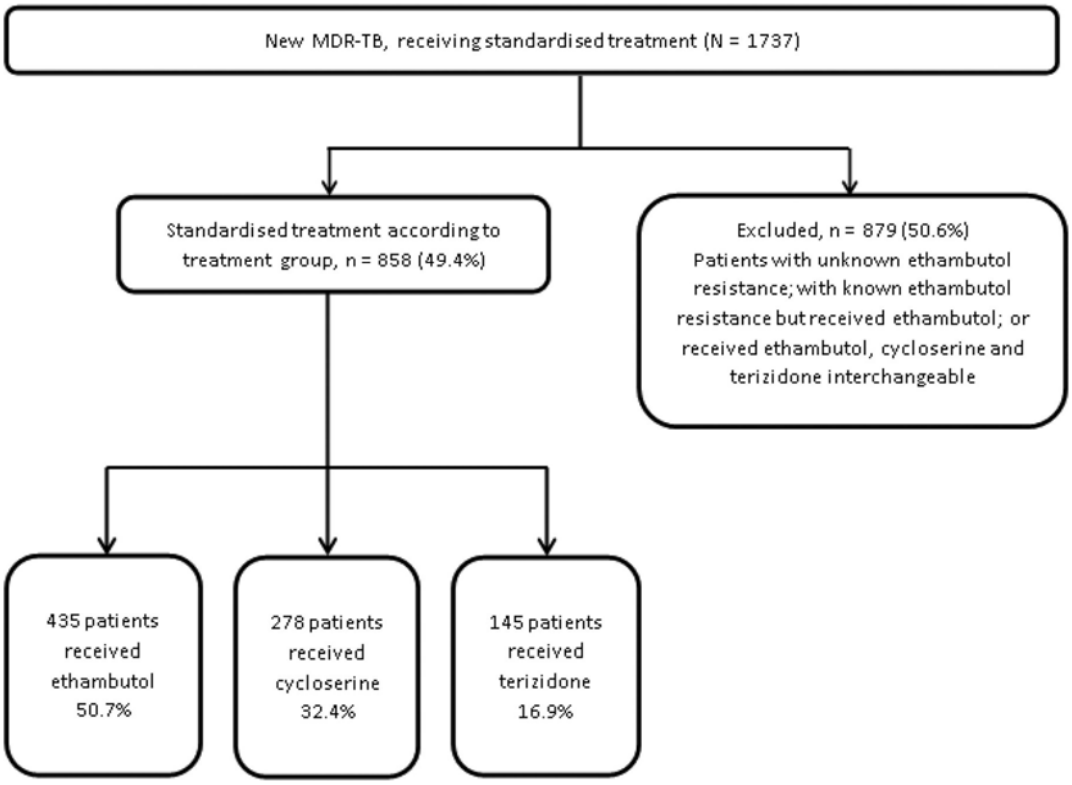

FIG 1 Enrolment of multidrug-resistant tuberculosis patients for standardized treatment under DOTS-Plus by ethambutol, cycloserine, and terizidone.

TABLE 1 Demographic and clinical characteristics of multidrug-resistant tuberculosis patients receiving ethambutol, cycloserine, or terizidone treatment as part of a standardized regimen (n 858)

Characteristic	Drug included in regimen			Total (*n* [%] = 858 [100.0])[a]	*P* value[b]
	Ethambutol (*n* = 435)	Cycloserine (*n* = 278)	Terizidone (*n* = 145)		
Gender (*n* = 857)					0.89
No. male	279	177	90	546 (63.7)	
No. female	155	101 (32.5)	55 (17.7)	311 (36.3)	
Mean age yrs (min–max); ±SD[f]	36.3 (18–69); ±11.0	36.3 (18–69); ±11.4	36.2 (18–73); ±11.5	36.3 (18–73); ±11.2	0.70
HIV status					0.30
No. negative	189	104	52	345 (40.2)	
No. positive	105	66	37	208 (24.2)	
No. unknown	141	108	56	305 (35.6)	
Extent of disease on chest x-ray at baseline (*n* = 568)					0.42
No. unilateral	42	25	19	86 (15.2)	
No. bilateral	220	174	88	482 (84.8)	
No. with previous TB (*n* = 826)					0.99
Yes	390	248	131	769 (93.1)	
No	29	18	10	57 (6.9)	
No. per wt category (kg) at baseline (*n* = 757)					0.63
>65	37	21	17	75 (8.7)	
≥50–65	188	111	58	357 (41.6)	
<50	159	103	63	325 (37.9)	
Mean wt at baseline (kg) (min–max); ±SD	52.8 (24–95); ±10.3	52.0 (30–104); ±10.6	51.9 (31–92); ±11.2	51.5 (24–104); ±10.6	0.48
% wt gained, mo 1–4 (*n* = 545) (no.)					0.19
>10	70	47	30	147 (27.0)	
>0–10	115	92	43	250 (45.9)	
wt loss	84	45	19	148 (27.1)	
Culture status at baseline (*n* = 807)					0.37
No. negative	62	31	14	107 (13.3)	
No. positive	357	224	119	700 (86.7)	
Serious adverse drug events (no.)					**0.055**
None	427	262	140	829 (96.6)	
Attributed to other drugs[c]	2	7	3	12 (1.4)	
Attributed to kanamycin/amikacin	6	9	2	17 (2.0)	
Culture conversion (no.) (*n* = 700)[d]					**0.002**
Yes	268	166	70	504 (72.0)	
Never	89	58	49	196 (28.0)	
Median time to conversion (wks)[e]; ± SD (range)	22.2; ±20.6 (1.7–110.7)	25.4; ±23.0 (2.4–107.6)	31.2; ±27.8 (3.3–99.9)	24.8; ±22.9 (1.7–110.7)	**0.001**[e]

[a]Column percentage. [b]Values in bold are significant. [c] Other drugs include ofloxacin, ethionamide, pyrazinamide, ethambutol/cycloserine/terizidone. [d]Patients with a positive culture at baseline. [e]Intergroup time to conversion. P value for ethambutol versus cycloserine, P 0.31; ethambutol versus terizidone, P 0.001; terizidone versus cycloserine, P 0.08. [f] SD, standard deviation.

Among patients presenting for treatment, few reported SADEs; 29 patients experienced SADEs (3.4%) overall, of which 17 (58.6%) were attributed to amikacin/kanamycin (Table 1). Of the remaining 12, 7/278 (2.5%) were among patients who received cycloserine, 3/145 (2.1%) were among those who received terizidone, and 2/435 (0.6%) were among patients who received ethambutol. This difference was marginally significant (P = 0.05).

Compared with HIV-uninfected patients, patients with known HIV infection were more likely to be lost to follow-up (odds ratio [OR], 0.6; 95% confidence interval [CI], 0.47 to 0.71; P < 0.001) or to die before the study ended (OR, 0.3; 95% CI, 0.24 to 0.41; P < 0.001) (data not shown).

Culture conversion

The cohort cure rate was 291 (33.9%) patients, 186 (21.7%) patients completed treatment, treatment failed in 83 (9.7%) patients, and 184 (21.5%) patients were lost to follow-up while 104

(12.1%) patients died (Table 1). Three quarters of patients who achieved culture conversion were eventually cured. Sixty percent of patients (167 or 86, respectively) who received either cycloserine or terizidone were successfully treated (cure or completed treatment) compared with 224 (51.9%) ethambutol patients. The loss to follow-up rate among ethambutol patients was 29.0% (126/435) compared with 14.7% (41/278) among cycloserine patients and 11.7% (17/145) among terizidone patients (Table 1). Compared to patients who received ethambutol, patients on cycloserine or on terizidone were significantly less likely to have an unfavorable outcome (30 to 40%), while HIV status and previous TB (Table 2; see also Table S2 in the supplemental material) were not associated with treatment outcome. Patients weighing <65 kg at baseline, who had not gained weight over the first 4 months of treatment, who failed to culture convert, or who had bilateral disease (Table 2; see also Table S2) had almost double the odds of an unfavorable outcome (OR, 1.94; P = 0.009; 95% CI, 1.18 to 3.22). In those patients in whom HIV status was known, sputum of HIV-infected patients was less likely to convert to negative on culture (OR, 1.4; 95% CI, 1.06 to 1.73; P = 0.015) (data not shown). Comparing cycloserine directly with terizidone, patients receiving cycloserine were significantly more likely to convert to culture-negative sputum (OR, 2.0; 95% CI, 1.26 to 3.18; P = 0.003) (data not shown).

TABLE 2 Unfavorable treatment outcomes among multidrug-resistant tuberculosis patients receiving standardized treatment by ethambutol, cycloserine, or terizidone

Variable	Successful outcome (n [%][a] = 477 [56.2])	Unfavorable outcome (n [%][a] = 371 [43.8])	Total no. (%)[b] (848 [100.0])	*P* value[c,d]
Gender (*n* = 847)				0.73
Male	305 (56.7)	233 (43.3)	538 (63.5)	
Female	172 (55.7)	137 (44.3)	309 (36.5)	
Mean age (yrs) (*n* = 841); min–max; ±SD[e]	36.8; 18.0–71.0; ±11.6	35.7; 18.0–73.0; +10.8	35.7; 18.0–73.0; ±11.2	0.14
HIV Status				0.47
Negative	201 (58.80)	141 (41.2)	342 (40.3)	
Positive	113 (54.9)	93 (45.1)	206 (24.3)	
Unknown	163 (54.3)	137 (45.7)	300 (35.4)	
Extent of disease on CXR (*n* = 564)				0.08
Unilateral	61 (70.9)	25 (29.1)	86 (15.2)	
Bilateral	266 (55.6)	212 (44.4)	478 (84.8)	
Previous TB (*n* = 816)				0.65
No	34 (59.6)	23 (40.4)	57 (7.0)	
Yes	29 (56.5)	330 (43.5)	759 (93.0)	
Wt category (kg) (*n* = 749)				**<0.001**
>65	55 (75.3)	18 (24.7)	73 (9.8)	
≥50-65	210 (59.5)	143 (40.5)	353 (47.1)	
<50	155 (48)	168 (52)	323 (43.1)	
% Wt gained during mo 1–4 (*n* = 549)				**0.04**
>10	94 (64.4)	52 (35.6)	146 (27.1)	
>0–10	156 (63.4)	90 (36.6)	246 (45.6)	
wt loss	76 (51.7)	71 (48.3)	147 (27.3)	
Conversion (*n* = 691)				**<0.001**
No	22 (11.4)	171 (88.6)	193 (27.9)	
Yes	359 (72.1)	139 (27.9)	498 (72.1)	
Drug included in regimen				**0.03**
Ethambutol	224 (51.8)	208 (48.2)	432 (50.9)	
Cycloserine	167 (60.3)	110 (39.7)	277 (32.7)	
Terizidone	86 (61.9)	53 (38.1)	139 (16.4)	

[a]Indicates the row percentage. [b]Indicates the column percentage. [c] Values in bold are significant. [d]The chi-square test was used. [e]SD, standard deviation.

For 700 patients (86.7%), baseline culture results were available: 504 (72.0%) achieved culture conversion. Mean time to culture conversion was 24.4 weeks (range, 1.7 to 110.7) (Table 1). The number of patients achieving culture conversion was significantly different among patients based on which of the three drugs was prescribed (Table 1 and Fig. 2). Fewer patients on terizidone converted

than those on ethambutol and cycloserine, and time to conversion was also longer. Patients whose sputum cultures converted to negative for Mycobacterium tuberculosis and those whose sputum failed to convert were similar in gender, age, and previous TB (see Table S3 in the supplemental material). Patients with bilateral disease were 50% less likely to achieve culture conversion (OR, 0.5; 95% CI, 0.25 to 0.986; P = 0.05) as were those who weighed <50 kg at baseline (OR, 0.52; 95% CI, 0.29 to 0.96; P = 0.04) or those who received terizidone treatment (OR, 0.47; 95% CI, 0.31 to 0.73; P = 0.001; see also Table S3). There was no significant difference in the outcomes of the different centers for the three different drugs for those centers where at least five patients had been enrolled in each arm of the analysis. While two centers had higher default rates than the remainder, this was independent of known HIV status (data not shown).

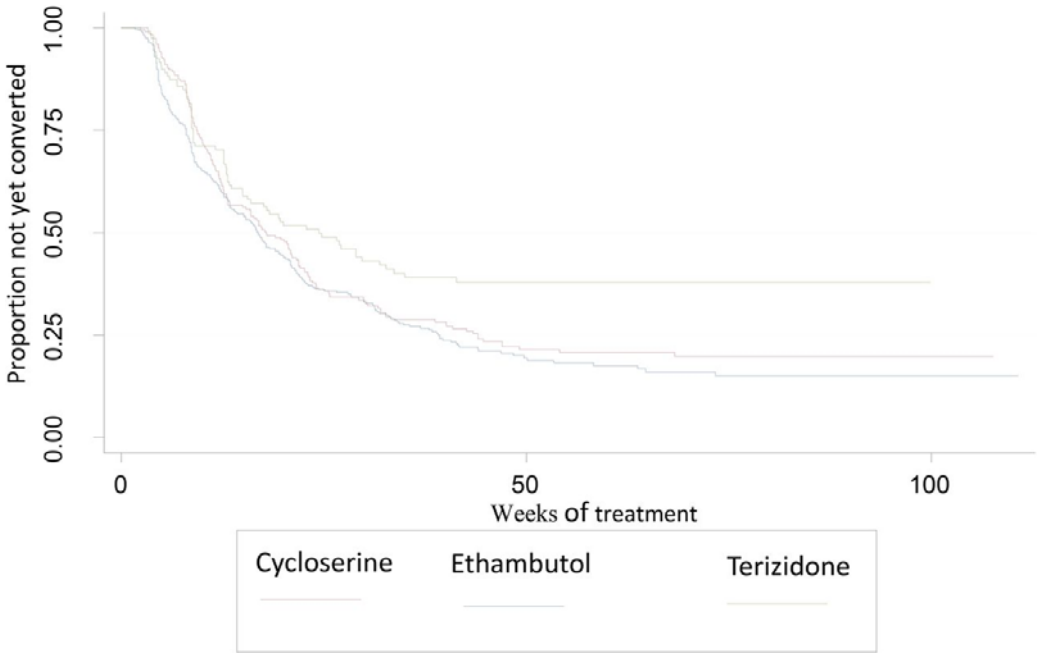

FIG 2 Kaplan-Meier graphs for culture conversion among multidrug-resistant tuberculosis patients who received ethambutol, cycloserine, or terizidone as part of a standardized regimen.

DISCUSSION

The South Africa (SA) DP cohort is, according to our knowledge, the only well-characterized cohort that has assessed cycloserine and terizidone as two distinct drugs and compared these with ethambutol against a standard background regimen. A considerable strength of our study is the large sample size, which included most of the MDR-TB patients treated in SA from 2000 to 2004 and with minimal variability in patient management protocols across sites and years. We found distinct differences in treatment outcomes, culture conversion, and SADEs between cycloserine, terizidone, and ethambutol. Treatment outcomes differed significantly among the three groups of patients (P < 0.001): the highest cure rate was among patients who received cycloserine (39%) compared with 32% of patients receiving ethambutol and 29% of those receiving terizidone. When compared to treatment with ethambutol, both patients receiving cycloserine or terizidone had a lower risk for unfavorable outcomes. The OR of patients on cycloserine was 0.71 (range, 0.52 to 0.96) and was 0.66 for those on terizidone (range, 0.45 to 0.99). On multivariate logistical regression, only terizidone was associated with a lower risk for unfavorable outcome (adjusted odds ratio [AOR], 0.4; range, 0.20 to 0.79). Conversely, for culture conversion, contrary results were found. Terizidone patients were significantly less likely to achieve culture conversion (unadjusted odds ratio [UOR],

0.47; 95% CI, 0.31 to 0.73) than patients who received either one of the two other drugs, and the time to conversion among terizidone patients was also significantly longer in comparison to cycloserine or ethambutol ($P < 0.004$). The few other studies comparing terizidone and cycloserine were small (23, 24). To our knowledge, there are no studies comparing the three drugs as we have here (17, 25). The explanation for the observed differences between cycloserine and terizidone is thus limited by the variables included in DP and other descriptive studies, and further work that better elucidates patient risk factors (e.g., epilepsy, HIV, alcohol use), the precise adverse events, and the time to adverse events is warranted.

Renewed interest in cycloserine and terizidone for inclusion in DR-TB regimens has resulted in more recent studies that have attempted to elucidate metabolic and pharmacokinetic efficiencies to guide optimal dosing strategies and assess potential drug interactions with other SLDs (26, 27). The pharmacokinetic/pharmacodynamic (PK/PD) characteristics of SLDs and their safety for prolonged use are generally not well studied, and the relationship with treatment outcome and culture conversion is poorly understood, though serum concentrations are expected to be a major contributor to treatment success (23, 25, 28–30). Terizidone, the dimer molecule, is cleaved into cycloserine molecules when metabolized by the body, but the dose equivalence after breakdown of cycloserine is unknown (4, 26, 27, 31).

More PK/PD studies over long sampling periods and among larger population sample sizes are needed to improve understanding of whether differences in dosing schedules can explain differences in culture conversion and treatment outcomes. Recent metanalyses suggest that the safety profiles of the two drugs are equivalent (19), which was not confirmed by our results. Even though we found few SADEs in the DP cohort, our data importantly contribute to the evidence comparing the safety profiles of the two drugs.

Our study has some limitations. A limitation of the DP cohort was that only the serious ADEs were recorded and low rates of ADEs to aminoglycosides suggest underreporting. However, there are differences between studies in how categories of ADEs are defined, which limits direct comparison of the safety of terizidone and cycloserine between cohorts (32–34). Further, even though the DP cohort was done as a prospective study and we had performed ongoing data verification, there were limitations related to data captured under routine program settings. In addition, we did not undertake to do pharmacokinetic studies, which limited the comparison of response to treatment and of ADEs. There was potential for bias in selection of patients offered any one of the three drugs, but the baseline clinical indicators of patients across the three drugs were similar and none of these were associated with the outcomes of interest; thus, we don't believe this would have affected the results. At the time of DP, TB and HIV management were not integrated, and we had limited data on HIV infection and antiretroviral therapy (ART) usage; thus, we could not explore if there was any interaction between ART and ethambutol, cycloserine, or terizidone. Current data suggest, however, that ART does not affect serum concentrations of ethambutol (35). Some evidence is available on ART-terizidone interaction, but data are conflicting and based on small numbers (27, 31, 36). This study was undertaken between 2000 and 2004 when ART was initially rolled out around South Africa (37); thus, it is possible that some of our HIV-infected patients who were lost to follow-up demised before they could complete treatment. It is also likely that toward the end of the trial the HIV-infected TB patients newly initiated on ART could have had higher death rates due, in part, to the complexities of immune reconstitution inflammatory syndrome (IRIS) (14, 16, 38) or alternatively due to other opportunistic infections, and this could bias the death rate of the cohort toward HIV (24).

In conclusion, high default rates in patients on ethambutol treatment detract from this drug's efficacy as an antituberculotic. The differences that we observed between cycloserine and terizidone require further elucidation. More patients on cycloserine than on terizidone achieved culture conversion to negative for M. tuberculosis, although the drugs appeared equivalent on treatment outcome. This suggests a need for further research on the PK/PD characteristics of the two drugs and optimal dosing strategies, how to render the drugs less toxic, and also how to determine if there are drug-drug interactions with antiretrovirals (ARVs).

MATERIALS AND METHODS

Study design and patients

DP was an observational prospective cohort study to determine the treatment outcomes of MDR-TB patients under programmatic management in SA. Adult patients over 18 years of age were enrolled from 2000 to 2004 (16) and received a standardized regimen. Dosing of the drugs was calculated according to patient weight, and the regimen consisted of an intensive phase of at least 4 months or until culture conversion was achieved (3, 16). This was followed by a continuation phase of 12 to 18 months. The regimen for the intensive phase consisted of an injectable second-line drug, viz. amikacin/kanamycin, pyrazinamide, ciprofloxacin/ofloxacin, ethionamide, and one of the following: ethambutol, terizidone, or cycloserine (assigned randomly). Pyrazinamide was stopped after the intensive phase. Dosages of the drugs are given in Table S1 in the supplemental material. All nine provinces of SA participated in DP. Monthly sputum specimens were collected from patients and cultured by the South African Medical Research Council TB laboratory (SAMRC). These data were used to calculate culture collection and treatment outcomes.

Patient demographic and clinical data were collected monthly in a standardized case record form (CRF), and SADEs were monitored and recorded as previously described (16, 34). The CRFs were captured into the Epi Info database v6.04 (Centers for Disease Control and Prevention, Atlanta, GA, USA), and data were exported to Stata Release 11 (StataCorp, College Station, TX, USA) for statistical analyses. Descriptive methods were used for describing the cohort as follows: the Pearson chi-square test for assessing associations with categorical variables and the Wilcoxon rank sum test for continuous variables. Probability (P) values were calculated at 95% confidence intervals (CIs) and a P value of <0.05 was taken as significant. Odd ratios (ORs) were calculated for the demographic and clinical variables that could impact on culture conversion and treatment outcomes. For multivariate analyses, the univariate variables with a P value of ≤ 0.2 were included. The final models were based on backwards elimination and controlled for gender and age. Standard treatment outcome and culture conversion definitions were used (39).

DP was approved by the Ethics Committee of the SAMRC and research committees of the nine provinces, and all patients gave written informed consent.

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