Clofazimine in the treatment of extensively drug-resistant tuberculosis with HIV coinfection in South Africa: a retrospective cohort study

N. Padayatchi[1]*, M. Gopal[2], R. Naidoo[1], L. Werner[1], K. Naidoo[1], I. Master[3] and M. R. O'Donnell[1,4]

[1]Centre for the AIDS Programme of Research in South Africa (CAPRISA), Nelson R. Mandela School of Medicine, Doris Duke Medical Research Institute, University of KwaZulu-Natal, Private Bag X7, Congella, 4013, South Africa; [2]Gulf Coast Pulmonary Medicine, Port Charlotte, FL 33952, USA; [3]King Dinuzulu Hospital, PO Box Dormerton 4015, South Africa; [4]Division of Pulmonary Medicine, Department of Internal Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA

*Corresponding author. Tel: +27-31-2604550; Fax: +27-31-2604549; E-mail: padayatchin@ukzn.ac.za

Background: Extensively drug-resistant (XDR) tuberculosis (TB) and HIV coinfection is associated with low cure rates and high mortality. Clofazimine has shown activity *in vitro* against *Mycobacterium tuberculosis*, but clinical experience with clofazimine in XDR-TB and HIV coinfection is limited.

Methods: This was a retrospective cohort study of adult XDR-TB patients in KwaZulu-Natal, South Africa, treated with either a clofazimine- or non-clofazimine-containing XDR-TB treatment regimen. The primary outcome measure was TB culture conversion at 6 months. Survival analysis and multivariate logistic regression compared time to event in different strata and identified risk factors for TB culture conversion.

Results: Between August 2009 and July 2011, eligible XDR-TB patients ($n=85$) were initiated on treatment for XDR-TB. Most patients (86%) were HIV-infected and receiving antiretroviral therapy (90%). Patients receiving a clofazimine-containing regimen ($n=50$) had a higher percentage of culture conversion (40%) compared with patients ($n=35$) receiving a non-clofazimine regimen (28.6%). On multivariate analysis, there was a 2-fold increase in TB culture conversion at 6 months (hazard rate ratio 2.54, 95% CI 0.99 – 6.52, $P=0.05$) in the group receiving a clofazimine-containing regimen. Adverse effects due to clofazimine were minor and rarely life-threatening.

Conclusions: Clofazimine was associated with improved culture conversion in the treatment of XDR-TB/HIV. Adverse effects were minor and non-life-threatening. Based on these preliminary data, further study of clofazimine in XDR-TB/HIV treatment is warranted. Given the present low rates of culture conversion in XDR-TB treatment, we recommend empirical inclusion of clofazimine in treatment regimens for XDR-TB.

Keywords: culture conversion, repurposed drugs, XDR-TB

Introduction

Increasing incidence of extensively drug-resistant (XDR) tuberculosis (TB)[1] has created a need for more effective treatment regimens,[2] especially in XDR-TB/HIV-coinfected patients in whom low cure and high mortality rates prevail.[3,4]

The protracted course of TB drug discovery has stimulated repurposing existing drugs, such as clofazimine. Clofazimine uniquely concentrates within macrophages, ideal for treating slow-growing organisms,[5,6] with demonstrated improved culture conversion in murine models and success in shortening treatment duration in a multidrug-resistant (MDR) TB case series.[7,8] Clofazimine has been incorporated into treatment guidelines for severe drug-resistant TB.[9] An XDR-TB systematic review demonstrated a treatment success rate of 66% with clofazimine-containing regimens.[10] However, published studies provide few data supporting its use in XDR-TB/HIV coinfection.[10–12]

We performed a retrospective cohort study to evaluate the effect of clofazimine-containing regimens on culture conversion in XDR-TB/HIV coinfection.

Methods

We reviewed the case records of patients ≥18 years with microbiologically confirmed XDR-TB, admitted to a specialist TB hospital in KwaZulu-Natal, South Africa, between August 2009 and July 2011. Patients were excluded if they had a history of XDR-TB treatment, clofazimine added to their regimen subsequent to treatment initiation or unavailable TB culture results.

Antimycobacterial treatment regimens, including clofazimine, were determined by treating physicians based on clinical judgement, susceptibility results and safety parameters.

Eligible patients were stratified into two treatment groups: those treated with a clofazimine-containing regimen (clofazimine group) and those treated without clofazimine (non-clofazimine group). Treatment regimens were tailored to the isolate's susceptibility. The clofazimine dosage used was either 200 or 300 mg daily based on weight,[13] with regimen change due to clofazimine-related adverse events noted.

Data collection

A standardized data extraction form was used. The variables collected are presented in Tables 1 and 2 and were obtained as part of standard clinical care.

Culture and drug susceptibility testing (DST)

Mycobacterium tuberculosis was cultured using BACTEC MGIT 960 (Becton Dickinson, Sparks, MD, USA) and 7H11 Middlebrook medium with DST by the 1% proportion method.[14]

Outcome, definitions and follow-up

Standard treatment outcome definitions as per Laserson *et al.*[15] were used. The primary outcome was time to culture conversion, which was defined as the time from treatment initiation to the date of the first of two consecutive negative cultures ≥1 month apart. Sputum outcomes were measured up to 12 months.

Statistical analysis

Comparisons between patients in both groups were performed using either Fisher's exact test (categorical data) or the Wilcoxon rank sums test (continuous data). Patients who did not culture convert were censored at their last follow-up visit (recorded by sputum collection dates). For the 6 month culture conversion analysis, time to conversion was censored at 6 months. Proportional hazards regression analyses were performed to assess factors associated with 6 month culture conversion.

Ethics approval

The study was approved by the Albert Einstein College of Medicine and the University of KwaZulu-Natal.

Results

During August 2009 to July 2011, 204 patients were admitted for XDR-TB treatment with culture-confirmed XDR-TB at baseline. Eighty-five patients met the inclusion criteria; 50 newly diagnosed with XDR-TB were treated with clofazimine ('clofazimine group') and 35 patients were treated with a non-clofazimine-containing regimen ('non-clofazimine group'). The remaining 119 patients were excluded: pre-XDR-TB ($n=18$); history of XDR-TB treatment ($n=30$) (excluded due to pre-exposure to study drugs); no *M. tuberculosis* culture ($n=16$); and clofazimine added to XDR-TB treatment ($n=55$).

Both groups were similar for baseline characteristics (Table 1).

Patients were followed for a maximum of 12 months after XDR-TB treatment initiation (median follow-up 7.7 months, IQR 5.3–11.8). Thirty of 85 patients (35.3%) culture converted. Median time to culture conversion was 13.5 weeks (IQR 8.9–20.4). In the clofazimine group, 20/50 (40%) patients culture converted and in the non-clofazimine group, 10/35 (28.6%) culture converted ($P=0.05$). Median time to culture conversion was 16.4 weeks (IQR 9.0–24.7) in the clofazimine group and 11.9 weeks (IQR

Table 1. Demographic and baseline characteristics of patients with XDR-TB treated with and without a clofazimine-containing regimen

Baseline characteristic	Overall ($n=85$)	Clofazimine group ($n=50$)	Non-clofazimine group ($n=35$)	P
Age (years), median (IQR)	34 (26–42)	34 (26–40)	36 (26–43)	0.79
Female, *n* (%)	55 (64.7)	34 (68.0)	21 (60.0)	0.49
HIV+, *n* (%)	73 (85.9)	44 (88.0)	29 (82.9)	0.54
On ARV[a] in HIV+, *n* (%)	64/71 (90.1)	41/44 (93.2)	23/27 (85.2)	0.41
Baseline CD4 count (cells/μL)[b], median (IQR)	221 (140–362)	185 (133–325)	250 (161–431)	0.22
Number of TB drugs[c], median (IQR)	8 (7–9)	8 (7–9)	7 (7–9)	0.09
Drugs used[c], *n* (%)				
pyrazinamide	83 (100)	49 (100)	34 (100)	1.00
capreomycin	82 (98.8)	48 (98.0)	34 (100)	1.00
ethionamide	82 (98.8)	49 (100)	33 (97.1)	0.41
moxifloxacin	82 (98.8)	48 (98.0)	34 (100)	1.00
para-aminosalicylic acid	79 (95.2)	46 (93.9)	33 (97.1)	0.64
terizidone	75 (90.4)	44 (89.8)	31 (91.2)	1.00
ethambutol	74 (89.2)	43 (87.8)	31 (91.2)	0.73
isoniazid	43 (51.8)	32 (65.3)	11 (32.4)	<0.01
amoxicillin/clavulanate	41 (49.4)	29 (59.2)	12 (35.3)	0.04
clarithromycin	26 (31.0)	15 (30.6)	11 (31.4)	1.00
rifampicin	2 (2.4)	0 (0.0)	2 (5.9)	0.16
ofloxacin	1 (1.2)	0 (0.0)	1 (2.9)	0.41

[a]Two patients did not have ARV status available.
[b]Baseline CD4 cells/μL data available for 58 patients only.
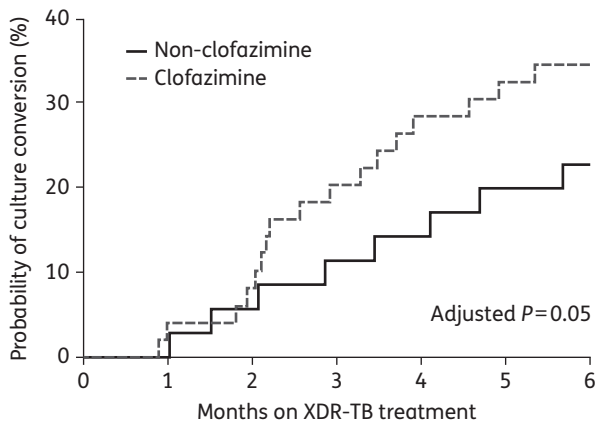[c]TB drug data available for 83/85 patients.

Figure 1. Cumulative incidence estimates of XDR-TB culture conversion in the clofazimine and non-clofazimine groups.

8.6–18.4) in the non-clofazimine group ($P=0.37$). In the first 2 months of treatment, there was no difference in the probability of culture conversion between groups. After 2 months, the probability of culture conversion was higher in the clofazimine group (Figure 1). By month 4, 32% of patients in the clofazimine group and 16% in the non-clofazimine group culture converted. In both groups, most culture conversions occurred within the first 6 months. In the clofazimine group, 18/20 culture conversions occurred before 6 months, while the remaining 2 converted before 12 months. Similarly, in the non-clofazimine group, 8/10 culture conversions occurred before 6 months and the remaining 2 before 12 months. Patients in the clofazimine group were twice as likely to culture convert within 6 months after XDR-TB treatment initiation. Year of starting XDR-TB treatment also had an impact on culture conversion. HIV status, antiretroviral (ARV), sex and age did not affect 6 month culture conversion (Table 2). Baseline chest radiograph (CXR) score was not associated with

Table 2. Predictors of 6 month culture conversion in XDR-TB in the clofazimine- and non-clofazimine groups

Variable	Number converted within 6 months (%)	Unadjusted hazard rate ratio (95% CI)	P	Adjusted hazard rate ratio (95% CI)	P
All patients					
age (per 10 year increase)		0.94 (0.63–1.39)	0.76		
gender					
female	17 (30.9)	1.00 (reference)			
male	9 (30.0)	0.92 (0.41–2.07)	0.84		
HIV status					
negative	3 (25.0)	1.00 (reference)		1.00 (reference)	
positive	23 (31.5)	1.23 (0.37–4.09)	0.74	1.10 (0.33–3.69)	0.88
baseline CD4 count (per 50 cells/μL increase)		1.01 (0.91–1.13)	0.83		
year initiated treatment					
2011	11 (27.5)	1.00 (reference)		1.00 (reference)	
2009 and 2010	15 (33.3)	1.27 (0.58–2.76)	0.55	2.02 (0.85–4.88)	0.11
clofazimine-containing group					
no	8 (22.9)	1.00 (reference)		1.00 (reference)	
yes	18 (36.0)	1.75 (0.76–4.02)	0.19	2.54 (0.99–6.52)	0.05
baseline CXR score[a] (per 10 unit decrease)		1.03 (0.91–1.17)	0.62		
change in CXR score from baseline to 6 months[a] (per 10 unit decrease)		1.46 (1.08–1.98)	0.02		
HIV-infected patients only					
age (per 10 year increase)		0.81 (0.50–1.33)	0.41		
gender					
female	15 (30.6)	1.00 (reference)			
male	8 (33.3)	1.04 (0.44–2.45)	0.93		
ARV status					
on ARVs	21 (32.8)	1.00 (reference)		1.00 (reference)	
not on ARVs	2 (28.6)	0.87 (0.21–3.73)	0.86	0.79 (0.18–3.43)	0.75
baseline CD4 count (per 50 cells/μL increase)		1.01 (0.91–1.13)	0.83		
year initiated treatment					
2011	8 (23.5)	1.00 (reference)		1.00 (reference)	
2009 and 2010	15 (38.5)	1.85 (0.78–4.36)	0.16	2.72 (1.03–7.14)	0.04
clofazimine-containing group					
no	8 (27.6)	1.00 (reference)		1.00 (reference)	
yes	15 (34.1)	1.31 (0.55–3.08)	0.54	2.02 (0.77–5.30)	0.15

[a]CXR score only available for 29 clofazimine group patients and none of the non-clofazimine group patients.

6 month culture conversion; however, change in CXR score by 6 months was statistically significant (Table 2).[16]

Among XDR-TB/HIV-coinfected patients, none of the baseline characteristics (Table 1) was associated with TB culture conversion at 6 months. Clofazimine showed a similar magnitude of effect as in the overall group, but this was not statistically significant. However, in the adjusted analysis, year of treatment initiation was significantly associated with culture conversion (Table 2). During 2009–11, the median number of TB medications patients received increased (*P*=0.02) as well as the proportion initiating ARVs (trend *P*=0.04).

Data regarding adverse reactions were available in 42/50 patients in the clofazimine group. Most patients (32/42) did not experience a clofazimine-related adverse reaction: 6 patients (14%) had a skin reaction; 3 (7%) had mild nausea and diarrhoea; and 1 became confused (2%). Clofazimine was discontinued in 3/10 patients due to severe vomiting (*n*=1), confusion (*n*=1) and skin discoloration (*n*=1). Most patients with adverse events were HIV infected.

Overall, 43.5% (37/85) died or were lost to follow-up and only 12.9% (11/85) were cured or completed treatment. There was no significant difference between the proportion of deaths in the clofazimine group versus the non-clofazimine group [36.0% (18/50) versus 54.3% (19/35), *P*=0.1212]. In the clofazimine group, 58.0% (29/50) were lost to follow-up and at the last visit, 50% (14/28) were still culture positive (median time of 7 months, range 3–15 months).

Discussion

We demonstrated that XDR-TB patients, the majority coinfected with HIV, are more than twice as likely to culture convert (hazard rate ratio 2.54, 95% CI 0.99–6.52, *P*=0.05) when treated with a clofazimine-containing regimen compared with patients treated with non-clofazimine-containing regimens in the same setting. Whilst few studies describe the effect of clofazimine in XDR-TB, even fewer report XDR-TB with HIV coinfection. In a long-term study of XDR-TB treatment elsewhere in South Africa, with lower HIV prevalence, clofazimine was an independent predictor of culture conversion.[4] Similar benefits were seen in HIV-uninfected patients in Shanghai and Bangladesh, with low treatment failure.[7,17]

The culture conversion rate in the clofazimine group was 40% compared with 28.6% in the non-clofazimine group (*P*=0.05). Although higher than the 20% culture conversion rates previously described,[18] it was lower than the 56.4% achieved in non-HIV settings.[17] In Bangladesh, the treatment of MDR-TB showed clofazimine-containing regimens were the most effective, with cure rates as high as 84.2% in an HIV-uninfected cohort.[7]

Time to culture conversion was shorter in the non-clofazimine group compared with the clofazimine group, although not statistically significant. In the first 2 months, there was no difference in culture conversion between the groups. After 2 months, the probability of culture conversion was higher in the clofazimine group. In both groups, most of the culture conversions occurred within the first 6 months. The delayed contribution of clofazimine may result from extensive binding and time required to accumulate in tissues, to reach binding saturation and then permit release of microbiologically active free drug. In addition, its ability to concentrate in macrophages and long half-life may result in sustained efficacy synergistic with pyrazinamide.[19]

Consistent with data from uncontrolled studies, HIV status, ARV and CD4 count did not affect *M. tuberculosis* culture conversion at 6 months.[3] Although there has been some suggestion of worse outcome with clofazimine in HIV-coinfected patients with XDR-TB,[4] this was not seen in our study. Our study demonstrates that clofazimine as part of a background treatment regimen improves *M. tuberculosis* culture conversion and has the potential to improve treatment outcomes in XDR-TB/HIV-coinfected patients. Early initiation of ART in MDR-TB patients has been shown to reduce mortality by 86%.[20] Integrated XDR-TB and HIV treatment will likely improve outcomes in dually infected patients. The limited data on radiological improvement may serve as a surrogate marker of culture conversion.

The optimal dose of clofazimine has not been defined. In this study, patients received either 200 or 300 mg of clofazimine daily,[13] higher than in other studies.[7,17] Few adverse events were reported even in HIV-infected patients, most of whom were also receiving an ARV, but these were minor with low treatment stoppages, similar to published reports.[11]

Our study has several limitations. The decision to initiate clofazimine treatment was made by the individual treating physician with no uniform criteria, thus selection bias may exist. Clofazimine susceptibility testing was unavailable. The review was limited to 12 months and the improved rates of culture conversion may not translate to improved cure at 24 months. Significant attrition in this cohort restricts inferences of final outcome.

The small sample and the retrospective analysis limit our study conclusion. Clofazimine was used as part of an individualized treatment regimen including on average six other medications, so outcomes cannot be definitively ascribed to clofazimine. Despite these limitations, our study adds important knowledge on the subject of clofazimine for the treatment of XDR-TB in a largely HIV-infected cohort, demonstrating improved culture conversion with minor adverse events.

In the absence of new drugs and effective treatment options, repurposing clofazimine as an additional drug for XDR-TB treatment increases therapeutic options, even in high HIV prevalence settings. Due to the paucity of clinical efficacy of clofazimine-containing regimens, the authors suggest the need for a controlled clinical trial.

Transparency declarations

None to declare.

References

1 WHO. *Global Tuberculosis Report 2013*. Geneva, Switzerland.

2 Zumla A, Nahid P, Cole ST. Advances in the development of new tuberculosis drugs and treatment regimens. *Nat Rev Drug Discov* 2013; **12**: 388–404.

3 O'Donnell MR, Padayatchi N, Kvasnovsky C et al. Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. *Emerg Infect Dis* 2013; **19**: 416–24.

4 Pietersen E, Ignatius E, Streicher EM et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet* 2014; **383**: 1230–9.

5 Cholo MC, Steel HC, Fourie PB et al. Clofazimine: current status and future prospects. *J Antimicrob Chemother* 2012; **67**: 290–8.

6 Wong EB, Cohen KA, Bishai WR. Rising to the challenge: new therapies for tuberculosis. *Trends Microbiol* 2013; **21**: 493–501.

7 Van Deun A, Maug AK, Salim MA et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010; **182**: 684–92.

8 Grosset JH, Tyagi S, Almeida DV et al. Assessment of clofazimine activity in a second-line regimen for tuberculosis in mice. *Am J Respir Crit Care Med* 2013; **188**: 608–12.

9 Caminero JA, Sotgiu G, Zumla A et al. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. *Lancet Infect Dis* 2010; **10**: 621–9.

10 Gopal M, Padayatchi N, Metcalfe JZ et al. Systematic review of clofazimine for the treatment of drug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2013; **17**: 1001–7.

11 Dey T, Brigden G, Cox H et al. Outcomes of clofazimine for the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis. *J Antimicrob Chemother* 2013; **68**: 284–93.

12 Hwang TJ, Dotsenko S, Jafarov A et al. Safety and availability of clofazimine in the treatment of multidrug and extensively drug-resistant tuberculosis: analysis of published guidance and meta-analysis of cohort studies. *BMJ Open* 2014; **4**: e004143.

13 National Department of Health, Republic of South Africa. *Management of Drug Resistant Tuberculosis Policy Guidelines*. Pretoria: Department of Health, Republic of South Africa. Updated January 2013.

14 Rusch-Gerdes S, Pfyffer GE, Casal M et al. Multicenter laboratory validation of the BACTEC MGIT 960 technique for testing susceptibilities of *Mycobacterium tuberculosis* to classical second-line drugs and newer antimicrobials. *J Clin Microbiol* 2006; **44**: 688–92.

15 Laserson KF, Thorpe LE, Leimane V et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005; **9**: 640–5.

16 Ralph AP, Ardian M, Wiguna A et al. A simple, valid, numerical score for grading chest X-ray severity in adult smear-positive pulmonary tuberculosis. *Thorax* 2010; **65**: 863–9.

17 Xu HB, Jiang RH, Xiao HP. Clofazimine in the treatment of multidrug-resistant tuberculosis. *Clin Microbiol Infect* 2012; **18**: 1104–10.

18 O'Donnell MR, Padayatchi N, Master I et al. Improved early results for patients with extensively drug-resistant tuberculosis and HIV in South Africa. *Int J Tuberc Lung Dis* 2009; **13**: 855–61.

19 Everitt D. Preclinical Assessment of Novel TB Regimens. *Presented at the Working Group on New TB Drugs Annual Meeting, Paris, 29 October 2013*. http://www.newtbdrugs.org/meetings/annual2013/downloads/presentations/13_D-Everitt_WGND_2013-v2.pdf (17 June 2014, date last accessed).

20 Padayatchi N, Abdool Karim SS, Naidoo K et al. Improved survival in multidrug-resistant tuberculosis patients receiving integrated tuberculosis and antiretroviral treatment in the SAPiT Trial. *Int J Tuberc Lung Dis* 2014; **18**: 147–54.