COMPARING MORTALITY AMONG HIV POSITIVE MDR-TB PATIENTS ON ARVS TREATED WITH EITHER MOXIFLOXACIN OR OFLOXACIN CONTAINING REGIMEN, GAUTENG, 2007 - 2012

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Background

Tuberculosis (TB) affects millions of people worldwide.[1] The WHO 2013 Global Tuberculosis report states that 8.6 million cases were diagnosed in 2012 of which 1.3 million deaths occurred.[1] Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis (TB) which shows resistance to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs.[1,2] South Africa (SA) is ranked as the world's third highest TB-burden country and fifth as a DR-TB burden country.[1,2] Additionally, SA carries the burden of especially serious Human Immunodeficiency Virus (HIV) and TB epidemics.[3] Currently, about 6 million people are living with the HIV and 2.4 million are on anti-retroviral drugs in SA and, despite being the leader in global HIV research, these epidemics continue to worsen leading to increase morbidity and mortality.[3]

The management of MDR-TB in South Africa is based on guidelines of the National Tuberculosis Control Programme (NTCP) and Directly Observed Therapy Short course (DOTS) expansion and enhancement strategy, 2013.[2,4] The current standardised regimen for the management of patients diagnosed with MDR-TB who have not been exposed to second line drugs is initiated into two phases at all designated facilities.[2,5] The first phase, known as intensive or injectable phase, involves a six-month period of five drugs kanamycin (or amikacin) by injection, a fluoroquinolone (FQN), ethionamide, terizidone and pyrazinamide.[1,2,4,5] The second phase, known as the continuation phase, uses an oral regimen only and is based on the use of four drugs: FQN, ethionamide, terzidone and pyrazinamide for a minimum of 18 months after TB culture conversion.[1,2,4,5] The FQNs are a backbone of the MDR regimen and, in 2010, ofloxacin was replaced with moxifloxacin in SA.[2]

Fluoroquinolones are a family of broad spectrum, systemic antibacterial agents that are being used in second phase therapy.[6,7] Moxifloxacin and ofloxacin are FQNs that are associated with better outcomes in the treatment of MDR-TB than treatment with a regimen not containing an FQN.[8-10] Moxifloxacin is an 8-methoxy-fluoroquinolone with a long plasma half-life of 11 hours.[6,7] It shows potent bactericidal and sterilizing activity against *Mycobacterium tuberculosis* (*Mtb*) in murine studies. Based on murine models, moxifloxacin has the ability to clear sputum bacilli (an indication of clearance of *Mtb* from the lungs) more quickly than other second-line anti-TB drugs.[6,7] Ofloxacin is a synthetic broad-spectrum antimicrobial agent administered orally

or by injection.[9] Pharmacokinetically, ofloxacin, a fluorinated carboxyquinolone, has a steady-state concentration, which is attained after four oral doses.[8] Following multiple oral doses at steady-state administration, the half-lives are approximately 4-5 hours for ofloxacin and 20-25 hours for moxifloxacin.[8] FQNs are associated with an increased risk of tendinitis and tendon rupture.[6] Generally, patients tolerate these medications satisfactorily, but serious adverse events can develop.

The aim of this study was to compare the respective mortalities of HIV-positive MDR-TB patients on ARVs receiving regimens containing either moxifloxacin or ofloxacin at Sizwe Tropical Diseases Hospital over a five -year period spanning 2007- 2012.

Methods

Setting and participants

The cohort study is a retrospective record review of medical and laboratory records of patients treated at Sizwe Tropical Diseases Hospital in Gauteng Province during the period 2007-2012. Sizwe Hospital is a specialised TB institution responsible for the management of drug-resistant TB patients. The hospital receives patients from the six districts of Gauteng Province as well as referral cases from other provinces. All HIV positive adults (over 18 years) with a laboratory confirmed diagnosis of MDR-TB and on ART were included. Patients were stratified into those on a moxifloxacin or ofloxacin-containing regimen.

Data collection

Data on patients who met the study criteria were initially extracted from the MDR-TB registers. Case record forms (CRFs) were used to enter socio-demographic, clinical and outcome information. Analysis was limited to medical records that were available from the hospital archives. CRFs were captured on Epi Info7® and rechecked for accuracy. Data was then exported to Microsoft Excel for further statistical analysis.

Statistical methods

We conducted a descriptive analysis to summarize socio-demographic factors relating to the study population. Logistic regression was used to determine factors associated with death. Kaplan-Meier survival curves were used to pictographically describe time-to-death. All statistical analyses were performed using STATA version 13 and a two-sided p-value of less than 0.05 was considered statistically significant.

Ethics approval

The Health Science Research Ethics Committee of the University of Pretoria approved the study (approval number: 430/2014). Approval was also obtained from the Gauteng Provincial Department of Health and Sizwe Hospital.

Results

Over the 5 year study period the total number of MDR-TB patients treated at Sizwe hospital was 4 363. All HIV positive MDR-TB on ARVs who were treated exclusively with either ofloxacin or moxifloxacin regimen were retained leaving with 927 medical records. Out of these, 169 records could not be found at the hospital archive. A total of 758 patient records was analysed. The median age of the patients was 37.9 years (range 18-69 years) and 396 (52%) were males (data not shown).

Among the study population, 405 patients (53.4%) received a moxifloxacin-containing regimen and 353 patients (46.6%) received an ofloxacin-containing regime. A total of 189 (24.9%) patients were cured and 206 (27.0%) completed the treatment course. Two hundred (26.4%) defaulted treatment and 124 (16.4%) died. The proportion that died was 18.4% among those on ofloxacin containing regimen compared with 14.7%

of the moxifloxacin containing regimen. Using multivariable analysis, patients on an ofloxacin regimen appeared 17% more likely to die. However, this was not statistically significant (Table 1).

In terms of mortality, patients who had a baseline body weight between 50-70kg were less likely to die than those who weighed less than 50kg (OR= 0.44, 95% CI 0.26 -0.76, p=0.003). The odds of dying when the CD4 count was >50 cells/mm^3 was 46% less compared to those who had a CD4 count of <50 cells/mm^3 (OR= 0.44, 95%CI 0.26 - 0.76, p= 0.003). The risk of dying was considerably higher in patients who did not culture convert, compared to those who converted (OR= 58.36, 95% CI=22.79- 149.47, p=0.001). Patients who reported as unemployed had an 82% higher risk of dying compared to those who were employed (OR=1.82, 95% CI 1.05-3.14, p=0.032) (Table 1).

Based on a Kaplan-Meier survival curve, patients treated with a moxifloxacin containing-regimen had a delayed time-to-death as compared to those treated with an ofloxacin-containing regimen - most notably before week 10 (Figure 1).

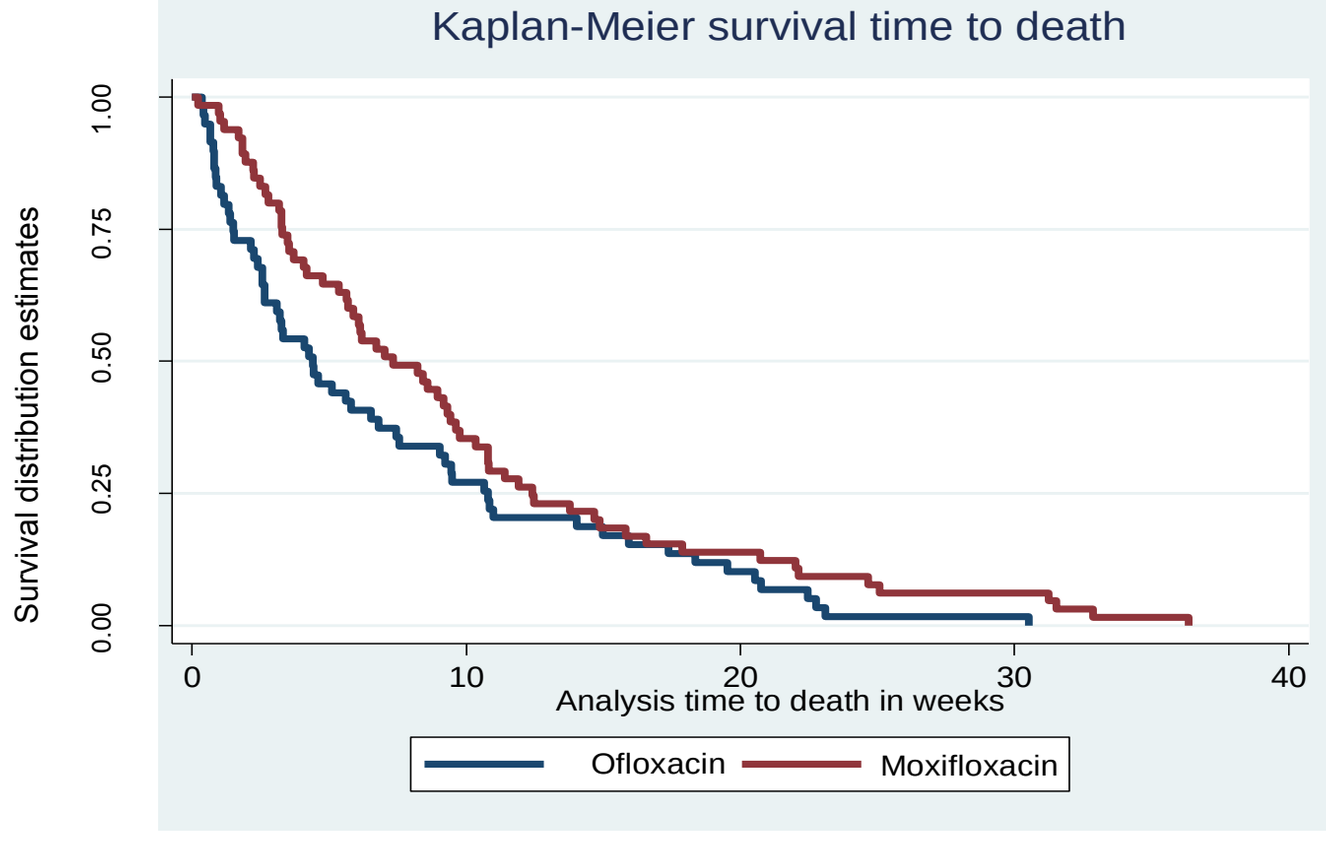

Figure 1: Time-to-death for patients treated with either moxifloxacin or ofloxacin containing regimen by time, among HIV positive MDR-TB patients at Sizwe Hospital, Johannesburg, South Africa, 2007 – 2012.

Table 1: Univariate and multivariate logistic regression model on mortality in Moxifloxacin and Ofloxacin treatment groups among HIV positive multidrug-resistant tuberculosis (MDR-TB) patients at Sizwe Hospital, Johannesburg, South Africa, 2007 – 2012.

Table		Univariate			Multivariate	
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Treatment regimen						
Moxifloxacin	1(Ref)			1(Ref)		
Ofloxacin	1.32	0.90 -1.95	0.154	1.17	0.71 - 1.93	0.54
Age category in years						
18-24	1(Ref)			1(Ref)		
25-34	1.84	0.69 - 4.90	0.225	2.011	0.51 - 6.74	0.258
35-44	1.44	0.54 - 3.85	0.471	1.65	0.49 - 5.59	0.419
45-54	1.33	0.47 - 3.77	0.591	1.18	0.32 - 4.35	0.803
55-64	0.81	0.79 - 3.69	0.79	0.13	0.01 - 2.05	0.148
65-74	omitted					
Gender				**NS**		
Female	1(Ref)					
Male	1.18	0.81 - 1.73	0.407			
Weight category [a]						
30 - 50 kg	1(Ref)			1(Ref)		
50 - 70 kg	0.56	0.37 - 0.84	0.005	0.44	0.26 - 0.76	0.003
70 - 90 kg	0.51	0.22 - 0.18	0.116	1.08	0.41 - 2.82	0.873
>90 kg	2.71	0.99 - 7.40	0.052	2.03	0.58 - 7.06	0.268
Cd4 count in cells/mm^3 [b]						
<50	1(Ref)			1(Ref)		
51-100	1.04	0.59 - 1.84	0.901	1.29	0.65 - 2..57	0.461
101-150	0.52	0.26 - 1.01	0.054	0.51	0.22 - 1.18	0.114
151-200	0.29	0.12 - 0.69	0.005	0.33	0.11 - 0.96	0.041
>250	0.32	0.18 - 0.58	0.001	0.46	0.23 - 0.92	0.028
Culture conversion						
Yes	1(Ref)			1(Ref)		
No	44.24	19.22 - 101.83	0.001	58.36	22.79 - 149.47	0.000
Patient category				**NS**		
New	1(Ref)					
Previously treated	0.99	0.67 - 1.47	0.962			
History of TB contact				**NS**		
None	1(Ref)					
Yes	1.12	0.73 - 1.71	0.612			
Adverse events				**NS**		
Not present	1(Ref)					
Present	1.22	0.63 - 2.37	0.547			
Alcohol intake				**NS**		
No	1(Ref)					
Yes	0.89	0.54 - 1.48	0.659			
Smoking				**NS**		
No	1(Ref)					
Yes	0.85	0.49 - 1.50	0.59			
Employment status						
Employed	1(Ref)			1(Ref)		
Unemployed	1.92	1.25 - 2.94	0.003	1.82	1.05 – 3.14	0.032
Infiltrates on Chest X-ray [c]				**NS**		
No	1(Ref)					
Yes	0.58	0.21 - 1.62	0.295			

Abbreviations: OR=Odds ratio; CI=Confidence interval; Ref=Reference; NS= Not significant
[a] Weight is defined as baseline weight as measured on admission by nurses
[b] Baseline CD4 count in cells/mm3 as confirmed by laboratory test on admission
[c] Infiltrates on chest x-ray was defined as chest x-ray taken on admission and interpreted by physician

Discussion

This study is the first to evaluate and report the outcomes of HIV positive MDR-TB on ARTs treated with regimens containing either moxifloxacin or ofloxacin in South Africa. Among the study cohort, mortality was not significantly different between the two study groups although time-to-death occurred earlier in those receiving an ofloxacin containing regimen. However, this was not clinically relevant as the difference in time-to-death was just a few weeks. *In vitro* studies from mice models have however shown that moxifloxacin is superior to other fluoroquinolones in in terms of outcome.[6] This disparity suggests that in clinical scenarios, factors other than drug choice are likely to be important.

Failure to convert was identified as a significant risk factor for mortality. In agreement with these findings, a study in KwaZulu-Natal Province showed an association between high mortality rate and culture non-conversion.[8] Reasons for this are unclear but possibilities could include undiagnosed additional drug resistance or other immunological deficiencies.

Patients with a CD4 count of less than 50 cells/mm^3 were three times more likely to die from MDR-TB compared to those with CD4 count greater than 250 cells/mm^3. This can be attributed to late ART initiation and late presentation for care. A previous policy on ART initiation was based on a threshold of <200 cells/mm^3, which may have contributed to the late initiation of ARTs.[10,11] Late presentation for care may also be attributed to centralised MDR-TB facilities in South Africa where patients may have had to wait for an available bed in order to be admitted for treatment initiation.[10] This situation should be addressed by changes in policy towards decentralization and deinstitutionalised treatment for MDR-TB.

A significantly higher mortality was observed in those weighing less than 50kg – a group presenting at an advanced stage of disease. The use of drugs containing 5 regimens as in this cohort is similar to a study conducted in Russia where these regimens reduced the incidence of mortality and treatment failure.[12] However, the use of a 5 or 6 drug regimen requires proper management of adverse events to ensure adherence to treatment especially when adults present with weight below 50kg. This is further complicated by the use of combination anti-retroviral regimens which, when combined, lead to a high pill burden inducing complex drug-drug interactions. Special attention in terms of individualised patient dosing with involvement of a pharmacist would be essential to provide safe and effective treatment and may mitigate some of the mortality risk.

This study had several limitations. Missing medical records, especially in the earlier years (2007-2009) meant that cases treated with ofloxacin were more likely to be missed. Furthermore, incomplete information about height measurement required for the calculation of the body mass index and unclear data recording for alcohol usage made it difficult to assess the significance of these variables. Final treatment outcomes of patients who were transferred from Sizwe Hospital were not available and could therefore not be included as a variable.

Conclusions

South Africa has amongst the highest TB and HIV prevalences in the world.[3,13] The converging dual epidemic of MDR-TB and HIV represents a growing threat to public health. Mortality was similar in both the moxifloxacin and ofloxacin treatment arms although there was a delay in time-to-death in the moxifloxacin group. Other factors such as degree of immune suppression and weight were shown to be very important factors influencing mortality beyond drug

selection. The use of moxifloxacin-containing regimens has been to be a good decision. However, special attention to individualised weight-based dosing and early management of MDR and HIV are essential to reduce mortality.

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