INT J TUBERC LUNG DIS 23(9):965–971

http://dx.doi.org/10.5588/ijtld.19.0053

Gatifloxacin is superior to levofloxacin and moxifloxacin in shorter treatment regimens for multidrug-resistant TB

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SUMMARY

SETTING: Data were collected from patients starting one of the shorter treatment regimens (STRs) for multidrug-resistant tuberculosis (MDR-TB) in Bangladesh, Niger or Cameroon.

OBJECTIVE: To estimate the effect of either a gatifloxacin (GFX), moxifloxacin (MFX) or levofloxacin (LVX) based STR on bacteriological effectiveness.

DESIGN: Retrospective study of prospectively collected data.

RESULTS: Among 1530 patients, bacteriological effectiveness was 96.7% overall. Stratified by treatment with a GFX-, LVX- or MFX-based regimen effectiveness was respectively 97.5%, 95.5% and 94.7%. Compared to those on a GFX-based regimen, the estimated summary odds ratio of having an adverse outcome was more than double (OR 2.05, 95% CI 1.09–3.90) in patients treated with either an LVX-based or MFX-based regimen. After adjusting for initial resistance, patients treated with an LVX-based regimen and MFX-based regimen had respectively a 4.5- and 8.4-fold times larger odds of an adverse bacteriological outcome. None among 859 patients at risk treated with a GFX-based compared to at least 4 of 228 among those on an MFX-based regimen acquired fluoroquinolone resistance.

CONCLUSION: GFX-based regimens had superior bacteriological effectiveness than MFX-based or LVX-based regimens. As GFX is currently unavailable in most MDR-TB programs, its reintroduction should be prioritised.

KEY WORDS: gatifloxacin; moxifloxacin; levofloxacin; core drug; bacteriological effectiveness

IN 2017, AN ESTIMATED 558 000 new cases of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) emerged worldwide, of whom only about a quarter were started on treatment and only half of the latter completed it successfully.[1,2] Between 1997 and 2007 patients in Bangladesh with MDR-TB and no history of prior treatment with second-line anti-TB drugs were sequentially enrolled on six standardised treatment regimens.[2,3] All but the last used ofloxacin (OFX) as the core drug, defined as the drug that drives the regimen and is indispensable for its efficacy.[4] In the optimised final 9-month regimen gatifloxacin (GFX) substituted OFX.[5] It was selected because a murine model had shown that sterilisation was achieved earlier with moxifloxacin (MFX) than with OFX. GFX belongs to the same generation as MFX, was off-patent and was locally available as an inexpensive good-quality generic product. The two compounds had then reportedly roughly equivalent activity.[6] After one year, the standard GFX dose was increased to high-dose as an *in vitro* experiment with MFX had shown that the selection of resistant mutants occurring with a standard dose was largely prevented when the dose was doubled.[7]

The 1.4% failures and 0.8% relapses testified to the high bacteriological effectiveness of the regimen.[2] Moreover, patients with low-level fluoroquinolone (FQ) resistance had a similarly favourable outcome as patients with FQ-susceptible TB.[2] After GFX was proscribed from Bangladesh, it was replaced by very high-dose levofloxacin (LVX), which was managerially simpler to use and probably as safe or safer than MFX.

Following this success, similar regimens were piloted in Cameroon and Niger (Table 1), with respectively standard- and high-dose GFX. In 2016, WHO recommended the "9-month Bangladesh regimen" as the "shorter MDR-TB regimen" (STR).[8] However, by then GFX had been removed in many countries following a report of its association with a higher dysglycaemia frequency than LVX or MFX among elderly patients treated for pneumonia in Canada.[9] In a 2016 document, WHO left the choice

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Article submitted 26 January 2019. Final version accepted 5 April 2019.

Table 1 Composition of shorter treatment regimens in different settings

Setting	Study type	FQ	Dose of the FQ	Intensive phase	Continuation phase
Bangladesh	Observational study	GFX	400 mg/d if ≥50 kg	4–6KmCfzGfxEHZPth	5GfxEZCfz
Bangladesh	Observational study	High-dose GFX	800 mg/d if ≥50 kg	4–6KmCfzGfxEHZPth	5GfxEZCfz
Bangladesh	Observational study	High-dose LVX	1750 mg/d if ≥65 kg	4–6 KmCfzLvxEHZPth	5LvxEZCfz
Niger	Observational study	High-dose GFX	800 mg/d if ≥50 kg	4–6KmCfzGfxEHZPth	8GfxEZCfz
Cameroon	Observational study	GFX	400 mg/d if ≥50 kg	4–6KmCfzGfxEHZPth	8GfxEZCfzP
Niger and Cameroon	Observational study	MFX	400 mg/d if ≥50 kg	4–6KmCfzMfxEHZPth	5MfxEZCfz

FQ = fluoroquinolone; GFX = gatifloxacin; Km = kanamycin; CFZ = clofazimine; E = ethambutol; H = isoniazid; Z = pyrazinamide; Pth = prothionamide; LVX = levofloxacin; MFX = moxifloxacin.

between MFX and GFX and their dosing to the implementing country.[10] A 2018 communication mentioned that LVX could substitute MFX if used under operational research conditions.[11]

The non-inferiority STREAM I (Short-course treatment for multidrug-resistant tuberculosis I) trial compared the Bangladesh STR with a conventional (long) WHO MDR-TB treatment control regimen.[12] Due to unavailability of prequalified GFX, high-dose MFX was used instead.[13] In an African multicountry observational study, in which Cameroon and Niger also participated, a standard 400 mg dose MFX was used.[14] Apart from Bangladesh,[3,15] there are, to our knowledge, no comparative studies assessing treatment outcome using different FQs as a core drug. Here we focus on the possible differences in bacteriological effectiveness of an STR regimen with the three FQs GFX, LVX or MFX, using data from Bangladesh, Cameroon and Niger.[2,3,16,17]

METHODS

Design

This retrospective study uses data collected under research protocols for the evaluation of program implementation of the STR in Bangladesh, Cameroon and Niger.

Table 2 Definitions of treatment outcomes

Treatment success: completion of the entire treatment duration without any positive culture at any time from the end of Month 5 onward to treatment completion, except for an (as defined) isolated positive culture

Failure: positive culture (any number of colonies) from any time from the end of Month 5 onward to the end of scheduled treatment duration, except for an (as per definition) isolated positive culture or confirming the isolated strain as genotypically different from the diagnostic strain

Relapse: recurrent tuberculosis with at least one positive culture after treatment cessation, except for an (as per definition) isolated positive culture or confirming the isolated strain as genotypically different from the diagnostic strain (used only in the Bangladesh data set)

Isolated positive culture: a single positive culture at any time from the end of Month 5 onward preceded by at least one negative culture and followed by at least two negative and no subsequent positive culture

Bacteriologically adverse outcome: failure (all three countries) or relapse (Bangladesh only)

Bacteriological effectiveness: the number with treatment outcome success divided by the same plus the number with a bacteriologically adverse outcome

Other outcomes (death and lost to follow-up) were excluded

Study population

Patients were included if they 1) had microbiologically confirmed pulmonary TB (on culture or molecular assay), 2) had genotypically or phenotypically resistance to at least rifampicin, 3) had received at least one day of either a GFX-, LVX- or MFX-based STR (Table 1), and 4) started treatment after 21 March 2005 and before 1 July 2017. Patients with a previous history of treatment for >1 month with second-line anti-TB drugs and those with clinical hepatitis at baseline had not been STR eligible under any of the three protocols. Patients were excluded from the analysis if the FQ was replaced or supplemented with bedaquiline, linezolid or delamanid.

Shorter treatment regimens

Table 1 shows regimens, type and dose of the FQ by site. The regimens were not adjusted to the initial drug resistance profile.

Data collection and analysis

Original data sets in EpiData or spreadsheet (Niger) file format were obtained from the data owners. A combined data set was created, using EpiData Analysis v2.2.3.187 (EpiData Association, Odense, Denmark; www.epidata.dk) for data set restructuring and primary analysis. Analyses requiring modelling techniques were performed with R software v3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

Outcomes were data-defined to satisfy uniform definitions (Table 2). To focus on bacteriological effectiveness, patients who were lost to follow-up, or died during treatment, were excluded. For Bangladesh both failures and relapses, while for Cameroon and Niger only failures were counted as adverse bacteriological outcomes to preclude duplicate reporting in a forthcoming publication on relapses in the 9-country African study.

FQ resistance detected on any phenotypic method overrode a susceptible result, categorised as 'high-level' if a strain grew on agar or Löwenstein-Jensen

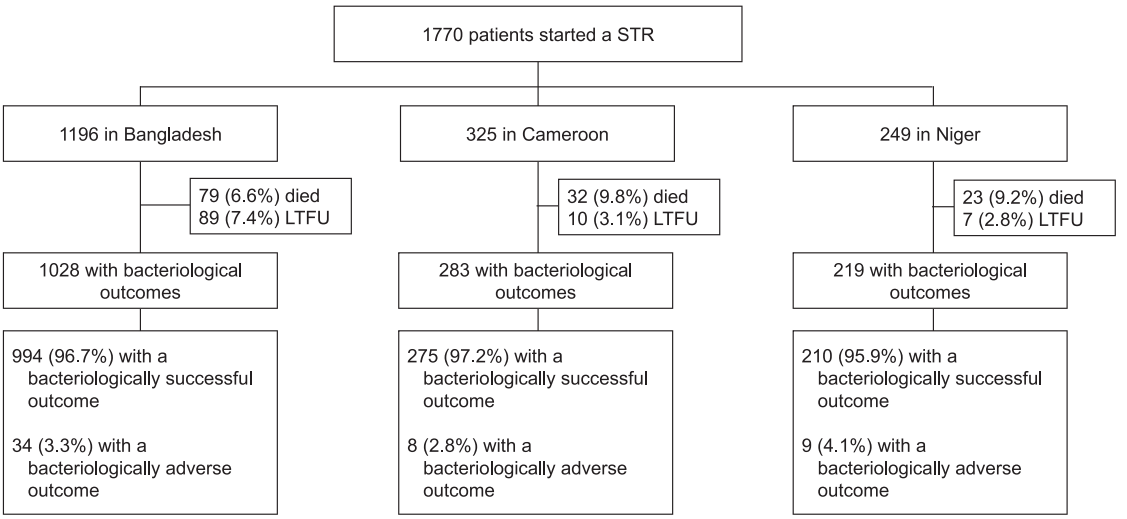

Figure 1 Flowchart showing patients with bacteriological outcomes in patients who started the STR for multidrug-resistant tuberculosis in Bangladesh, Cameroon and Niger. STR = shorter treatment regimen; LTFU = lost to follow-up.

medium at ≥8 mg/l OFX or if the minimum inhibitory concentration (MIC) for GFX was ≥2 mg/l.

Analysis

Characteristics and bacteriological outcomes of patients enrolled were stratified by core drug.

The effect of the FQ choice on the binary outcome success vs. non-success was estimated in a multivariable logistic regression model adjusting for initial FQ and kanamycin (KM) resistance, known predictors of having a bacteriologically unfavourable outcome. The base model, which also included sex, age and human immunodeficiency virus (HIV) status, was simplified using stepwise elimination. To obtain a valid non-zero value for the referent in the determination of the relative frequency of acquired FQ resistance we used Bayesian estimation with 100 000 iterations where indicated.

We summarised the data using meta-analysis across the three settings, defining the GFX arm as control and the LVX and MFX arms as experimental. To allow the effect to vary beyond the sample error in the three settings, we gave preference to a random effects model to estimate the odds of having an adverse treatment outcome among patients in an experimental arm contrasted with those in the control arm.

Ethics

Data collection in Cameroon and Niger was defined by study protocols previously approved by national ethics review bodies and The Union Ethics Advisory Group.[14,16] Data from the Damien Foundation supported Bangladesh MDR-TB programme are covered by a study protocol previously approved by the National Research Ethics Committee of Bangladesh Medical Research Council and the Institutional Review Board of the Institute of Tropical Medicine Antwerp. All patients completed and signed an informed consent form in the local language before starting treatment.

RESULTS

During the study period, 1770 patients started an STR: 1196 (67.6%) in Bangladesh, 325 (18.4%) in Cameroon, and 249 (14.1%) in Niger (Figure 1). The proportions of patients who had respectively died or were lost to follow-up were 6.6% and 7.4% in Bangladesh, 9.8% and 3.1% in Cameroon, and 9.2% and 2.8% in Niger. The remaining 1530 (86.4%) patients with a bacteriologically defined outcome were retained for analysis.

Of the 1530 patients, 978 were treated with GFX, 262 with MFX, and 290 with LVX as the core drug (Table 3). Overall, 68.2% of patients were male. As no HIV testing was performed in Bangladesh, the majority of patients had unknown HIV status.

The initial DST result for FQ or KM was unknown in respectively 7.1% and 7.0%. The majority (40 of 51) of patients with a bacteriologically adverse outcome had both an initial and a failure/relapse DST result. Initial resistance to KM was very rare. Low- and high-level FQ resistance was identified in respectively 5.6% and 3.1% of all patients.

Overall, bacteriological effectiveness was 96.7% and stratified by GFX-, LVX- and MFX-based regimen 97.5%, 95.5%, and 94.7%, respectively (Table 3). Of 85 patients with low-level and 47 patients with high-level FQ resistance, 83.5% and 57.4% were treated successfully (Table 4). In the 85 patients with low-level FQ-resistant TB, treatment success was 91.3% (42/46), 76.5% (26/34) and 60.0% (3/5) when treated with respectively a GFX-based, LVX-based and MFX-based regimen (P = 0.072) (data not shown in the table).

Table 3 Description of the data set by core drug

	GFX		LVX		MFX		Total	
Characteristic	*n*	col%	*n*	col%	*n*	col%	*n*	col%
Total	978		290		262		1530	
Country								
Bangladesh	738	75.5	290	100.0	0	0	1028	67.2
Cameroon	134	13.7	0	0	149	56.9	283	18.5
Niger	106	10.8	0	0	113	43.1	219	14.3
Outcome								
Success	954	97.5	277	95.5	248	94.7	1479	96.7
Non-success	24	2.5	13	4.5	14	5.3	51	3.3
Age, years								
Q 1: 6–24	273	27.9	57	19.7	42	16.0	372	24.3
Q 2: 25–31	243	24.8	71	24.5	70	26.7	384	25.1
Q 3: 32–42	231	23.6	54	18.6	86	32.8	371	24.2
Q 4: 43–96	231	23.6	108	37.2	64	24.4	403	26.3
Sex								
Female	308	31.5	100	34.5	79	30.2	487	31.8
Male	670	68.5	190	65.5	183	69.8	1043	68.2
HIV status								
Negative	204	20.9	0	0	218	83.2	422	27.6
Positive	30	3.1	0	0	44	16.8	74	4.8
Not recorded	744	76.1	290	100.0	0	0	1034	67.6
Fluoroquinolone*								
Susceptible	859	87.8	203	70.0	228	87.0	1290	84.3
Resistant low	46	4.7	34	11.7	5	1.9	85	5.6
Resistant high	43	4.4	0	0.0	4	1.5	47	3.1
Missing	30	3.1	53	18.3	25	9.5	108	7.1
Kanamycin*								
Susceptible	944	96.5	236	81.4	237	90.5	1417	92.6
Resistant	5	0.5	1	0.3	0	0	6	0.4
Missing	29	3.0	53	18.3	25	9.5	107	7.0

* Initial isolate.
Fluoroquinolone resistance was categorised as 'high-level' if strains grew on agar or Löwenstein-Jensen medium at ≥8 mg/l ofloxacin or if the minimum inhibitory concentration for GFX was ≥2 mg/l.
GFX = gatifloxacin; LVX = levofloxacin; MFX = moxifloxacin; Q = quartile; HIV = human immunodeficiency virus.

Compared to treatment with a GFX-based regimen, and after adjusting for initial resistance to FQ and KM, patients treated with an LVX-based regimen and MFX-based regimen had respectively a 4.5-fold (adjusted odds ratio [aOR] 4.5; 95% confidence interval [CI] 1.7–11.9) and 8.4-fold (aOR 8.4, 95% CI 3.4–22.6) higher odds of having an adverse bacteriological outcome (Table 4). Other predictors of adverse outcomes included initial low-level FQ resistance (aOR 16.0, 95% CI 6.8–37.9) and initial high-level FQ resistance (aOR 122.1, 95% CI 47.9–343.4).

Of 1290 patients with an initially FQ-susceptible strain, 17 had an adverse bacteriological outcome. Of the 17, 12 also had a FQ DST result at the point of failure/relapse. Among these 12, 0/2 patients on a GFX-based regimen but 2/5 on the LVX-based and 4/5 on an MFX-based regimen did acquire FQ resistance (Table 5). Per 1000 patients with initially FQ-susceptible MDR-TB initiated on treatment and with bacteriologically defined outcome, the relative frequency of acquired FQ resistance was largest for MFX, intermediate for LVX and lowest for GFX, with the confidence interval not overlapping between the estimates for MFX and GFX.

One of the three GFX-treated patients with initially FQ-susceptible TB had a missing DST result at the point of failure/relapse (Table 5). As worst-case scenario, we forced this case to be a missed case of acquired FQ resistance in a sensitivity analysis while maintaining the best-case scenario that none of the four MFX-treated with missing DST result at the point of failure/relapse was actually a missed case of acquired FQ resistance. In frequentist analysis, the recalculated CI for the GFX-treated (1.2% acquired

Table 4 Bivariate and multivariate summary of characteristics significantly determining outcome

	Non-success						
Characteristic	*n*	row%	Success *n*	Total *n*	OR	aOR (95% CI)	*P* value
Total	51	3.3	1479	1530			
Core drug							
Gatifloxacin	24	2.5	954	978	1	1	
Levofloxacin	13	4.5	277	290	1.9	4.5 (11.9–1.7)	0.0020
Moxifloxacin	14	5.3	248	262	2.2	8.4 (22.6–3.4)	<0.0001
Fluoroquinolone*							
Susceptible	17	1.3	1273	1290	1	1	
Resistant low	14	16.5	71	85	14.8	16.0 (37.9–6.8)	<0.0001
Resistant high	20	42.6	27	47	55.5	122.1 (343.4–47.9)	<0.0001
Missing	0	0	108	108	—	—	—
Kanamycin							
Susceptible	48	3.4	1369	1417	1	1	
Resistant	3	50.0	3	6	28.5	2.5 (16.0–0.41)	0.30
Missing	0	0	107	107	—	—	—

* Fluoroquinolone resistance was categorised as 'high-level' if strains grew on agar or Löwenstein-Jensen medium at ≥8 mg/l ofloxacin or if the minimum inhibitory concentration for GFX was ≥2 mg/l.
In addition to the variable of interest, initial fluoroquinolone and KM resistance (known predictors of having a bacteriologically unfavourable outcome) were included in the saturated multivariable model, as well as age, sex and HIV status. As age, sex and HIV status were not significantly associated with the outcome, they are not shown in the simplified multivariable model.
OR = odds ratio; aOR = adjusted OR; CI = confidence interval; HIV = human immunodeficiency virus.

Table 5 Frequency of acquired FQ resistance during treatment of patients with ofloxacin-susceptible TB with a shorter treatment regimen of multidrug-resistant TB by core drug

		Acquired FQ resistance[3]					Bayesian estimation		
Core drug	FQ-susceptible (A)[1] *N*	Data missing[2] *n*	No *n*	Yes (B) *n*	(B/A) *1 000	95% CI	Mean[4]	95% CrI[4]	Probability[5]
Total	1 290	5	6	6	4.7	2.1–10.0	5.0	1.6–8.9	
GFX	859	1	2	0	0.0	0.0–4.5	0.6	0.0–2.2	1
LVX	203	0	3	2	9.9	2.7–35.2	12.3	0.7–27.3	0.9930
MFX	228	4	1	4	17.5	6.8–44.2	19.7	4.2–37.8	0.9996
Sensitivity analysis									
GFX	859	0	2	1	1.2	0.2–6.6	1.7	0.0–4.5	1
LVX									0.9762
MFX									0.9982

[1] At treatment start. Patients with initial FQ resistance ($n = 132$) or missing result ($n = 108$) excluded.
[2] No susceptibility test result available at point of failure/relapse.
[3] From FQ-susceptible to FQ-resistant among failures (all three settings) and relapses (Bangladesh only).
[4] Estimated from 100 000 simulations.
[5] Probability of a more likely occurrence of a bacteriologically adverse outcome with that drug compared to GFX.
FQ = fluoroquinolone; TB = tuberculosis; CI = confidence interval; CrI = (Bayesian) credibility interval; GFX = gatifloxacin; LVX = levofloxacin; MFX = moxifloxacin.

resistance, 95% CI 0.2–6.6) did still not overlap that of the MFX-treated (17.5%, 95% CI 6.8–44.2). While the credibility interval with Bayesian estimation showed minor overlap, the probability that the MFX-associated frequency of acquired resistance was worse than the GFX-associated was 99.8% (Table 5).

In a summarising meta-analysis the heterogeneity ($I = 2\%$) across the three study sites was very low. It showed that in each of the three settings the likelihood of having an adverse bacteriological treatment outcome tended to be higher in patients on either LVX-based or MFX-based regimen than those on a GFX-based regimen (Figure 2), but not significantly so in each setting on its own. While a fixed-effects model gives, by definition, tighter confidence intervals, we preferred the more conservative estimate obtained from the random effects model.[18] The thus estimated summary OR of having an adverse outcome was more than double (OR 2.05, 95% CI 1.09–3.9) in patients treated with either an LVX-based or MFX-based regimen.

DISCUSSION

In a large patient population of 1530 cases from Bangladesh, Cameroon and Niger, the overall bacteriological effectiveness of the STR was 96.7%. This compares favourably with the 87.8% bacteriological effectiveness of the conventional long MDR-TB treatment regimen reported in a meta-analysis using data from 25 countries.[19]

Our study adds comparative information on bacteriological effectiveness of using either GFX, LVX or MFX as core drug in the STR. Using a conservative approach, we demonstrate that patients treated with a GFX-based regimen are more likely to have a bacteriologically successful treatment outcome than patients treated with an LVX- or MFX-based regimen. Across the settings the odds were overall twice as large for treatment failure or relapse when either an LVX- or MFX-based STR was used. This effect remains strong after adjusting for initial FQ and KM resistance. It is also remarkable that no patient in the large GFX cohort acquired FQ resistance, while acquisition of resistance was associated with the other two FQs, most notably with MFX.

Our previous study had unequivocally shown that a GFX-based STR was superior to different OFX-based regimens.[3] Until now, there has been little other clinical evidence to make a choice between GFX, LVX and MFX when constituting an MDR-TB treatment regimen. Long MDR-TB treatment regimens showed similar conversion frequency and treatment outcomes, irrespective of whether LVX or MFX was used.[20,21]

Initial FQ resistance was strongly associated with a

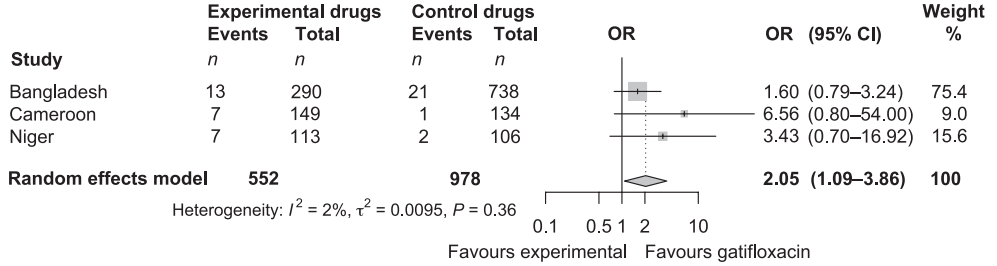

Figure 2 Summary of meta-analysis. Gatifloxacin is defined as the "control" drug, levofloxacin and moxifloxacin are the "experimental" drugs. The weight is defined by inverse variance weighting. OR = odds ratio; CI = confidence interval.

poorer bacteriological outcome in our study. Patients with low- and high-level FQ resistance were treated successfully in respectively 83.5% and 57.4%. However, patients with low-level FQ-resistant TB were more likely to have a successful treatment outcome when GFX, rather than LVX or MFX, was used. These findings extend on earlier ones showing that high-level initial FQ resistance was frequently associated with adverse outcomes, while low-level resistance could largely be overcome with a high dose of GFX.[2] The use of normal-dose MFX rather than high-dose GFX may have contributed to the higher failure frequency in the 9-country African study.[14] In mice, high-dose (800 mg/kg) MFX was effective for the treatment of low-level but not for high-level MFX-resistant TB.[22] Pharmacodynamic hollow-fibre model studies, assessing the microbial killing by GFX, LVX and MFX, have shown a similar ranking as our study, i.e., GFX > LVX > MFX.[23] The only study using high-dose MFX is the STREAM Phase I clinical trial showed even higher frequencies of bacteriological adverse outcomes and acquired FQ resistance.[24] Moreover, the frequency of QT interval prolongation was twice as large with the high-dose MFX-based STR than with the WHO MDR-TB treatment regimen.[24] These data suggest that a high-dose MFX STR has no or little advantage compared to the normal-dose MFX STR used in Cameroon and Niger.[14]

Our findings show that retracting GFX from MDR-TB treatment was an unfortunate decision. The initial withdrawal by the company was triggered by a Canadian study[9] finding a higher dysglycaemia frequency with GFX than with MFX among elderly patients treated for pneumonia.[25] It is doubtful whether findings from these patients, much older and likely with a higher body mass index than most MDR-TB patients, are transferable to the latter. Dysglycaemia is easy to identify and has been rare in MDR-TB programmes.[2,16,17] When identified in patients on GFX, it was successfully managed.[17,25] The simplicity for glycaemia monitoring contrasts with the complexity of conducting electrocardiograms, recommended when prescribing MFX, particularly when combined with other cardiotoxic drugs, or when using a high dose. Therefore, re-introducing GFX into MDR-TB treatment would seem to be a rational course of action.[26]

One of the strengths of this study is that it reflects operational field implementation in three MDR-TB treatment programmes. Furthermore, simultaneous individual patient analysis combining data from three sites increases power while the consistency of the findings without heterogeneity strengthens the conclusions obtained from meta-analysis. Encoded data were verified continuously for completeness and coherence by experts in the field of MDR-TB.

There are also limitations to consider. In Cameroon and Niger, the continuation phase of the GFX-based regimen was extended from 5 to 8 months, which could have further reduced the already low GFX relapse rate with standard 9-month duration,[27] but relapses were not considered in any arm in these two countries. The use of isoniazid (high-dose vs. normal-dose) and prothionamide (only in the intensive phase vs. throughout) differed by setting (Table 1). However, previous studies have shown that initial resistance to isoniazid and prothionamide has little effect on bacteriological treatment outcome compared to FQ resistance, suggesting that any such difference is primarily explained by the type and dose of FQ.[14] Data on initial resistance were missing for a minority of patients. As this happened randomly, it is unlikely to have resulted in bias.

The very low frequency of bacteriologically adverse outcomes among cases with FQ-susceptible TB treated with high-dose GFX, its retained effectiveness against low-level resistant strains, and the virtual absence of acquired FQ resistance all suggest that GFX is a highly effective anti-TB core drug, and much more so than LVX or MFX. Our findings suggest that GFX is thus likely the preferred FQ of choice for the STR. We feel justified to suggest safeguarding bedaquiline-based regimens, the currently third and last option in the TB treatment cascade, for patients failing a FQ-based regimen or patients with demonstrated initial high-level FQ resistance.[4]

CONCLUSION

The data from three different MDR-TB programmes show that high-dose GFX-based regimens are bacteriologically superior to normal-dose MFX-based or high-dose LVX-based regimens. Acquired FQ resistance in patients treated with GFX is so rare that resistance is unlikely to spread quickly and the drug can probably remain the core drug of uncomplicated MDR-TB for years to come. Although GFX is not currently available in most MDR-TB programmes, our findings reinforce the call for its reintroduction into MDR-TB treatment.[26]

Conflicts of interest: none declared.

Note added in proof: In the Bangladesh jurisdiction, a 2018 national policy change required replacing high-dose LVX with high-dose MFX for the treatment of RR-TB. There were four treatment failures in the cohort of the first 69 sputum smear-positive patients, all of which were due to acquired fluoroquinolone resistance. This reinforces independently the hierarchy of bacteriological effectiveness of gatifloxacin > levofloxacin > moxifloxacin observed in this study.

References

1 World Health Organization. Global tuberculosis report, 2018. WHO/CDS/TB/2018.20. Geneva, Switzerland: WHO, 2018.
2 Aung K J M, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis

among over 500 consecutive patients. Int J Tuberc Lung Dis 2014; 18: 1180–1187.
3 Van Deun A, Aung K J M, Halim M A, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010; 182: 684–692.
4 Van Deun A, Decroo T, Piubello A, de Jong B C, Lynen L, Rieder H L. Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs. (Perspective). Int J Tuberc Lung Dis 2018; 22: 239–245.
5 Nuermberger E L, Yoshimatsu T, Tyagi S, et al. Moxifloxacin-containing regimen greatly reduces time to culture conversion in murine tuberculosis. Am J Respir Crit Care Med 2004; 169: 421–426.
6 Ginsburg A S, Grosset J H, Bishai W R. Fluoroquinolones, tuberculosis, and resistance. Lancet Infect Dis 2003; 3: 432–442.
7 Gumbo T, Louie A, Parsons L M, Salfinger M, Drusano G L. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an in vitro pharmacodynamic infection model and mathematical modeling. J Infect Dis 2004; 190: 1642–1651.
8 World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update. WHO/HTM/TB/2016.04. Geneva, Switzerland: WHO, 2016.
9 Park-Wyllie L Y, Juurlink D N, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med 2006; 354: 1352–1361.
10 World Health Organization. Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions. Geneva, Switzerland: WHO, 2016.
11 World Health Organization. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). WHO/CDS/TB/2018.18. Geneva, Switzerland: WHO, 2018.
12 Nunn A J, Rusen I D, Van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials 2014; 15: 353.
13 Moodley R, Godec T R. Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials. Eur Respir J 2016; 25: 29–35.
14 Trébucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. Int J Tuberc Lung Dis 2018; 22: 17–25.
15 Van Deun A, Hamid Salim M A, Kumar Das A P, Bastian I, Portaels F. Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh. Int J Tuberc Lung Dis 2004; 8: 560–567.
16 Kuaban C, Noeske J, Rieder H L, Aït-Khaled N, Abena Foe J L, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis 2015; 19: 517–524.
17 Piubello A, Hassane Harouna S, Souleymane M B, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis 2014; 18: 1188–1194.
18 Schwarzer G, Carpenter J R, Rücker G. Meta-analysis with R (use R!). Heidelberg, Germany: Cham Springer International Publishing, 2015.
19 Ahmad N, Ahuja S D, Akkerman O W, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data analysis. Lancet 2018; 392: 821–834.
20 Koh W J, Lee S H, Kang Y A, et al. Comparison of levofloxacin versus moxifloxacin for multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2013; 188: 858–864.
21 Lee J, Lee C H, Kim D K, et al. Retrospective comparison of levofloxacin and moxifloxacin on multidrug-resistant tuberculosis treatment outcomes. Korean J Intern Med 2011; 26: 153–159.
22 Poissy J, Aubry A, Fernandez C, et al. Should moxifloxacin be used for the treatment of extensively drug-resistant tuberculosis? An answer from a murine model. Antimicrob Agents Chemother 2010; 54: 4765–4771.
23 Deshpande D, Pasipanodya J G, Mpagama S G, et al. Levofloxacin pharmacokinetics/pharmacodynamics, dosing, susceptibility breakpoints, and artificial intelligence in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis 2018; 67(Suppl 3): S293–S302.
24 Nunn A J, Phillips P P J, Meredith S K, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med 2019; 380: 1201–1213.
25 Chiang C Y, Van Deun A, Rieder H L. Gatifloxacin for short, effective treatment of multidrug-resistant tuberculosis. (Perspective). Int J Tuberc Lung Dis 2016; 20: 1143–1147.
26 Chiang C Y, Trébucq A, Piubello A, Rieder H L, Van Deun A. Should gatifloxacin be included in the model list of essential medicines? (Correspondence). Eur Respir J 2018; 51: 1702329.
27 Fox W, Ellard G A, Mitchison D A. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999; 3(Suppl 2): S231–S279.

RÉSUMÉ

CONTEXTE : Les données ont été recueillies auprès de patients qui commençaient l'un des régimes de traitement plus courts (STR) de la tuberculose multirésistante (TB-MDR) au Bangladesh, au Niger ou au Cameroun.

OBJECTIF : Estimer l'effet d'une STR à base de gatifloxacine (GFX), de moxifloxacine (MFX) ou de lévofloxacine (LVX) sur son efficacité bactériologique.

MÉTHODE : Ceci est une étude rétrospective de données recueillies de façon prospective.

RÉSULTATS : Chez 1 530 patients, l'efficacité bactériologique était de 96,7% dans l'ensemble. Stratifiée par traitement avec respectivement un régime à base de GFX, LFX ou MFX, l'efficacité était de 97,5%, 95,5% et 94,7%. Comparativement à ceux qui suivaient un traitement à base de GFX, le rapport de cotes sommaire estimatif des effets indésirables était plus du double (OR 2,05 ; IC 95% 1,09–3,90) chez les patients traités par un traitement à base de LVX ou MFX. Après ajustement pour tenir compte de la résistance initiale, les patients traités avec un traitement à base de LVX et un traitement à base de MFX avaient respectivement 4,5 et 8,4 fois plus de chances d'obtenir un résultat bactériologique indésirable. Aucun des 859 patients à risque traités par un traitement à base de GFX n'a acquis de résistance à la fluoroquinolone, comparativement à au moins 4 des 228 patients traités par un traitement à base de MFX.

CONCLUSION : Les régimes à base de GFX avaient une efficacité bactériologique supérieure à celle des régimes à base de MFX ou de LVX. Comme le GFX n'est actuellement pas disponible dans la plupart des programmes de MDR-TB, sa réintroduction devrait être prioritaire.

RESUMEN

MARCO DE REFERENCIA: Se recogieron datos de pacientes que iniciaban un esquema terapéutico más breve contra la tuberculosis multirresistente (MDR-TB) en Bangladesh, Níger o Camerún.

OBJETIVO: Evaluar el efecto de los esquemas terapéuticos más breves, ya sea basados en gatifloxacina (GFX), moxifloxacina (MFX) o levofloxacina (LVX), sobre la efectividad bacteriológica.

MÉTODO: Fue este un análisis retrospectivo de datos recogidos de manera prospectiva.

RESULTADOS: En 1530 pacientes la efectividad bacteriológica global fue 96,7%. Al estratificar los datos por tipo de esquema, la efectividad fue 97,5% con la pauta basada en GFX, 95,5% con LVX y 94,7% con el esquema basado en MFX. En comparación con las personas que recibieron la pauta con GFX, el cociente de posibilidades combinado de presentar una reacción adversa fue más del doble en los pacientes tratados con la pauta basada en LVX o MFX (OR 2,05; IC 95% 1,09-3,90). Al corregir en función de la resistencia inicial, las posibilidades de un desenlace bacteriológico adverso fueron 4,5 veces superiores en los pacientes tratados con una pauta basada en LVX y 8,4 veces superiores en los que recibieron la pauta con MFX. No se observó resistencia adquirida a las fluoroquinolonas en ninguno de los 859 pacientes expuestos tratados con el esquema basado en GFX, en comparación con al menos cuatro casos en los 228 pacientes que recibieron un esquema basado en MFX.

CONCLUSIÓN: La efectividad bacteriológica de los esquemas basados en GFX es superior a la de los esquemas que contienen MFX o LVX. Dado que el GFX no está actualmente disponible en la mayoría de los programas de MDR-TB, es importante dar prioridad a su reintroducción.