Predictive factors of QT prolongation in the Short regimen for the STREAM 1 trial

Gareth Hughes, Claire Cook, Saiam Ahmed, Andrew Nunn and Sarah Meredith on behalf of the STREAM collaboration.

MRC Clinical Trials Unit at UCL , Institute of Clinical Trials & Methodology, 90 High Holborn 2nd Floor London WC1V 6LJ

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Introduction

STREAM 1 was a randomised phase 3 trial in rifampicin-resistant participants comparing a 9-11 month Short regimen to a 20-24 month Long regimen following WHO 2011 guidelines. Recruitment was from sites in South Africa, Ethiopia, Vietnam and Mongolia. Severe QT prolongation (DAIDS ≥ Grade 3) was more frequent on the Short regimen, and was defined as QT or QTcF ≥500 ms (11% v 6.4%) OR an increase ≥60ms above baseline (64% v 41%). These differences may be due to high dose moxifloxacin (mfx) and clofazimine (cfz) in the Short regimen. All patients in the long regimen received a fluoroquinolone at standard dose We explored additional predictive factors for development of severe QT prolongation.

Methods

Trial participants had regular ECG monitoring for up to 52 weeks after randomisation. The 282 participants randomised to the Short regimen were analysed to identify factors associated with severe QT prolongation using Pearson's chi-squared test and a two-sample t test. Analysis was completed using ***Stata*** (R).

Risk factors for the both groups included a baseline QT/QTcF >450ms and recruitment from the Mongolia site. To a lesser extent increased age and lower creatinine were associated with increased risk for the ≥500ms group and lower BMI was associated with an increased risk in the ≥60ms change from baseline group.

		% with QT/QTcF ≥500ms at any point	n / N	HR (95% CI)	P value	Multivariable analysis adjusted HR (95% CI)
Country	Ethiopia	**3.53**	3 / 85	**1.00** (base)	-	**1.00** (base)
	Vietnam	**7.58**	5 / 66	**2.20** (0.52-9.23)	**0.278**	**1.53** (0.32-7.22)
	South Africa	**11.11**	12 / 108	**3.48** (0.98-12.3)	**0.053**	**5.45** (1.17-25.21)
	Mongolia	**45.45**	10 / 22	**16.87** (4.63-61.4)	**<0.001**	**12.40** (3.07-49.95)
Baseline QT/QTcF	0-399 ms	**3.28**	4 / 122	**1.00** (base)	-	**1.00** (base)
	400-449 ms	**14.40**	22 / 153	**4.59** (1.58-13.34)	**0.005**	**3.56** (1.21-10.47)
	≥450 ms	**80.00**	4 / 5	**40.27** (10.04-161.44)	**<0.001**	**78.20** (17.27-353.9)
Age		**10.60**	30 / 282	**1.04** (1.01-1.07)	**0.008**	**1.04** (1.01-1.08)
Creatinine		**11.10**	30 / 268	**0.98** (0.95-0.99)	**0.023**	

Table 1. Univariate analysis of risk factors for a QT/QTcF ≥500 ms in the Short regimen group

		% with QT/QTcF ≥60ms change from baseline	n / N	HR (95% CI)	P value	Multivariable analysis adjusted HR (95% CI)
Country	Ethiopia	**64.70**	55 / 85	**1** (base)		**1** (base)
	Vietnam	**63.60**	42 / 66	**1.13** (0.76-1.69)	**0.532**	**1.04** (0.69-1.57)
	South Africa	**56.80**	62 / 109	**1.02** (0.71-1.47)	**0.912**	**1.32** (0.84-2.09)
	Mongolia	**90.90**	20 / 22	**3.83** (2.26-6.49)	**<0.001**	**4.86** (2.77-8.52)
Baseline QT/QTcF	0-399 ms	**93.80**	168 / 179	**1 (base)**		**1** (base)
	400-449 ms	**5.02**	9 / 179	**0.52** (0.26-1.01)	**0.054**	**0.51** (0.26-0.99)
	≥450 ms	**1.10**	2 / 179	**6.01** (1.47-24.54)	**0.012**	**5.58** (1.33-23.30)
BMI		-	179	**0.95** (0.91-0.99)	**0.028**	**0.93** (0.88-0.98)

Table 2. Univariate analysis of risk factors for a QT/QTcF ≥60 ms change from baseline in the Short regimen group

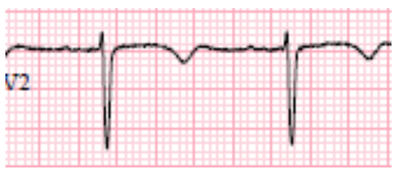

Fig1. ECG from patient with QTcF of 536ms at week 12.

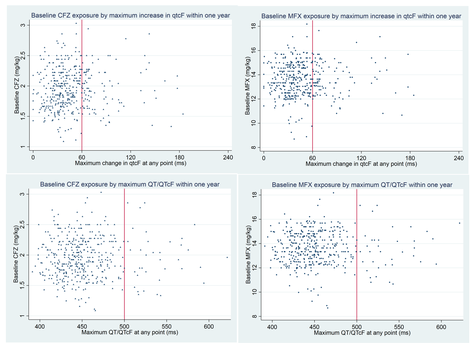

Fig 2.Baseline mfx and cfz dose (mg/kg) and relationship to maximum QTcF increase and maximum QT/QTcF absolute values

Results

Of the 282 participants in the short regimen, 182 had severe QT prolongation on at least one ECG; 30 had QT/QTcF of ≥500ms and 179 an increase of ≥60ms from baseline after monitoring up to the point participants had a treatment change of more than 1 drug.

The median time to a QT prolongation of ≥500ms or an increase of ≥60ms from baseline was 20 weeks (IQR 8.0 to 28 weeks) for both groups. The median change was 104ms (IQR 83 to 137) in those with QT/QTcF ≥500ms and 67ms (IQR 63-77) in those with ≥60ms increase from baseline.

There was no significant association with gender, hypokalaemia, diabetes or HIV infection. Baseline mg/kg dose of mfx and cfz did not appear to increase risk of QT prolongation ≥500ms or ≥60ms above baseline (Fig4). QT/QTcF of ≥500ms was observed more frequently in those starting on 800mg mfx compared to those on 600mg (10% v 12%) this was not apparent in those who had >60ms increase from baseline (66% v 62%).

Conclusions

- Whilst the baseline QT/QTcF level may be expected to influence whether it later increased, the reason for increased risk of patients from Mongolia was unclear, possibly due to genetic or environmental differences affecting pharmacodynamics of the trial medications.
- The baseline dose in mg/kg for either moxifloxacin or clofazimine was not found to be associated with a risk of severe QT prolongation.
- Although 2 patients developed a QTcF >500ms within 4 hours of their 1st dose of medication the median time of 20 weeks suggests the change takes several weeks; 80% occurred at 8 weeks or later.

Tel. +44 020 7670-4700 | gareth.hughes@ucl.ac.uk |