

Treatment of multidrug-resistant tuberculosis in children and adolescents with a 9-month regimen in Africa

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Childhood TB working group meeting

Liverpool, 26 October 2016



Background

- Until 2016, WHO-recommended regimens for the treatment of multi-drug resistant tuberculosis (MDR-TB) were long (>20 months) and had low cure rates (<55%)
- In 2010, Van Deun et al. reported 88% [83% - 92%] cured without relapse in 206 patients treated by a 9-month regimen 4 KmGfxPtoHCfzEZ/5GfxCfzEZ in Bangladesh.
- An observational study was launched in 2013 in francophone Africa to determine the effectiveness and tolerance of a modified “Bangladesh” regimen for MDR-TB
4KmMfxPtoHCfzEZ / 5MfxCfzEZ

Objectives

Although the observational study only included adults, the Bangladesh regimen was used for children and adolescents aged < 18 years in the participating countries

The objectives of the work presented here are

- To determine the effectiveness of this shorter regimen in children and adolescents
- To document its adverse drug events

Methods (1)

- 9 countries of francophone Africa participated : Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Côte d'Ivoire, DR Congo, Niger, Rwanda
- 1,006 adult patients were included in the study between 1st January 2013 and 31st March 2015 (27 months)
- Data were collected over the same period on **all children and adolescents < 18 years** treated with the Bangladesh regimen who had met the following criteria :
 - Bacteriologically confirmed TB (microscopy, Xpert or culture)
 - Confirmed rifampicin resistance (RR) by molecular or phenotypic drug susceptibility test
 - No history of treatment by 2nd line drugs

Methods (2)

- Patients managed within the framework of the National Tuberculosis Program (hospital-based, ambulatory or mixed)
- Strict daily Directly Observed Treatment conducted throughout treatment
- Monthly clinical, biological and bacteriological (smear and culture) examinations during treatment and 6-monthly after treatment termination
- DST was performed on initial strains and if strains were isolated at 6 months of treatment or later

Study population

- 72 confirmed RR-TB cases were diagnosed during the study period in patients <18 years
 - 13 could not be retrieved or died
 - 1 was started on a long regimen
 - 58 were started on Bangladesh regimen, of whom 47 were recruited early enough for cohort analysis

Characteristics		N (%)
Age group	0-9 years	5 (11%)
	10-14 years	10 (21%)
	15-17 years	32 (68%)
Sex	Female	23 (49%)
New case	Yes	17 (36%)
HIV infected	Yes	9 (19%)

Drug dosages (mg/kg)used

Drug	Min	p25	Median	p75	Max
Kanamycine	12.5	14.2	16.7	18.1	26.3
Prothionamide	8.6	12.3	13.2	16.3	31.2
Isoniazid	5.0	8.0	10.0	11.1	15.0
Moxifloxacin	5.2	7.1	9.5	10.5	16.7
Clofazimine	1.3	1.8	2.4	2.6	3.8
Ethambutol	10.5	17.5	19.0	20.0	30.0
Pyrazinamide	21.1	24.1	27.8	30.0	50.0

Treatment outcome

Outcome	N=47	%
Cured	27	57.4%
Treatment completed	12	25.5%
Success	39	83.0%
Failure	3	6.4%
Died	4	8.1%
Lost to follow-up	1	2.5%

Definitions following 2013 WHO recommendations with

Cure = treatment termination without evidence of failure and ≥ 3 consecutive negative cultures after the last positive

Failure = any positive culture at 6 months or later (except if preceded by ≥ 1 and followed by ≥ 2 negative cultures)

Treatment outcome according to age & HIV

Success rate was similar in children under 10 years of age (80%) and in older children / adolescents (83%)

Outcome	HIV + N=9	HIV - N=38
Success	7 (78%)	32 (84%)
Failure	0	3 (8%)
Died	2 (22%)	2 (5%)
Lost to follow-up	0	1 (3%)

Among patients who survived, treatment success did not differ significantly by HIV status: 100% in HIV-positive and 89% in HIV-negative patients

Adverse events / biological abnormalities

Type	No. assessed	n	%
Gastro-intestinal	38	28	74%
Hepatic	37	3	8%
Neurological	38	4	11%
Renal	38	0	0%
Auditive	37	15	41%

- All adverse drug event were mild / moderate (grade<3)
- Kanamycin was given intermittently or stopped < month 4 for 4/15 patients with reported audition problem

Discussion

- All patients <18 years (except 1) were treated by the short regimen in the participating countries, which minimized selection bias
- Information was abstracted from patient's cards and was sometimes incomplete
- Sample size was small, and very few patients were aged less than 10 years, thus caution should be taken before generalizing results

Conclusion

- Outcomes appeared excellent in the few children and adolescents with bacteriologically-confirmed MDR-TB treated with the Bangladesh regimen
- Treatment success was high in HIV-infected patients
- All adverse events / biological abnormalities reported during treatment were mild, none resulted in discontinuation of treatment
- These results should encourage to apply the short regimen to children and adolescents