

## Extensively drug-resistant tuberculosis: experience at the Tuberculosis Research Centre, Chennai, India

A. Thomas, P. Joseph, D. Nair, D. V. B. Rao, V. V. B. Rekha, N. Selvakumar, K. Jaggarajamma, R. Balambal  
Tuberculosis Research Centre (Indian Council of Medical Research), Chennai, India

### SUMMARY

Ten extensively drug-resistant tuberculosis (XDR-TB) patients were identified among 104 human immunodeficiency virus negative multidrug-resistant tuberculosis (MDR-TB) patients treated at the Tuberculosis Research Centre, Chennai, India, in two different cohorts between 1999–2003 and 2006–2007. They were managed with individualised treatment regimens. At the time of diagnosis of MDR-TB, one patient had XDR-TB and three had initial ofloxacin resistance. One patient who had

had a lobectomy in addition to chemotherapy became bacteriologically negative, three died, three defaulted and the remaining three, who are bacteriologically positive, are still continuing treatment. Although based on a small number of patients, our results have not been encouraging.

**KEY WORDS:** tuberculosis; drug resistance; XDR-TB; second-line drugs; management

THE WORLD HEALTH ORGANIZATION (WHO) Global Task Force defined extensively drug-resistant tuberculosis (XDR-TB) in October 2006 as multidrug-resistant TB (MDR-TB) with resistance to any one of the fluoroquinolones (FQs) and at least one of the injectable drugs (kanamycin [KM], amikacin [AMK] and capreomycin [CPM]).<sup>1</sup> Since then, at least one case has been reported from 58 countries,<sup>1</sup> including India.<sup>2,3</sup> The magnitude of the problem is not known due to the paucity of laboratories capable of conducting quality-assured drug susceptibility testing (DST) against second-line drugs (SLDs). The Tuberculosis Research Centre is a WHO-recognised supranational reference laboratory for mycobacteriology where DST for SLDs (KM, ofloxacin [OFX] and ethionamide) is performed. During the period 1999–2003, the policy in this centre was to treat MDR-TB patients with a FQ-containing regimen, with streptomycin or KM and three other SLDs, depending on the DST results. DST was performed at the time of diagnosis and during treatment whenever a positive culture was isolated. Patients with MDR-TB are currently being treated with the DOTS-Plus regimen recommended by India's Revised National TB Control Programme.\*<sup>4</sup>

\*6/9KOEthCsEthZ/18OEthCsE; K = kanamycin, O = ofloxacin, Eth = ethionamide, Cs = cycloserine, Eth = ethambutol, Z = pyrazinamide. Numbers before the letters indicate the duration in months of the phase of treatment.

We report the occurrence of XDR-TB and its management in a selected cohort.

### METHODOLOGY

The case records of patients admitted for MDR-TB treatment were reviewed retrospectively for the emergence of XDR-TB. Patients belonged to two cohorts, the first from the Tiruvallur District (1999–2003)<sup>2</sup> and the second from the Tiruvallur and Chennai Corporation (2006–2007). Sputum DST results were classified using the international definitions for resistance to SLDs,<sup>2</sup> and patients with XDR-TB were identified. Patients in the first cohort were treated with individualised regimens that included three new drugs that the patient had not received earlier from among AMK, gatifloxacin, para-aminosalicylic acid, augmentin (amoxicillin and clavulanic acid), metronidazole and clofazimine. From 2007 onwards, moxifloxacin, CPM and clarithromycin were also added. During treatment, progress was monitored by clinical, bacteriological, biochemical and haematological evaluations at monthly intervals. The treatment regimens were modified when patients did not respond or developed intolerance to any of the drugs. Patients were referred for surgical treatment if needed.

Ethics committee approval was not required for this retrospective analysis.

Correspondence to: Aleyamma Thomas, Tuberculosis Research Centre (Indian Council of Medical Research), Mayor V R Ramanathan Road, Chetput, Chennai 600 031, India. Tel: (+91) 44 2836 9540. Fax: (+91) 44 2836 2528. e-mail: aleyamma\_01@yahoo.co.in

Article submitted 17 August 2010. Final version accepted 1 April 2011.

**Table 1** Details of emergence of XDR-TB among the cohort of MDR-TB patients in relation to initial OFX and or KM resistance

	1999–2003 Cohort I	2006–2007 Cohort II	Cured		Failed		Death		Default	
			Cohort I	Cohort II	Cohort I	Cohort II	Cohort I	Cohort II	Cohort I	Cohort II
MDR-TB patients, <i>n</i>	66	38	25	26	17	6	8	3	16	3
OFX resistance at start of MDR-TB treatment	4	6	2	3	2	1	0	2	0	0
KM resistance at start of MDR-TB treatment	1	1	0	0	0	0	0	1	0	1
Pre-treatment XDR-TB	1	0	0	0	0	0	0	0	0	0
KM- and OFX-susceptible XDR-TB	60	31	23	23	15	5	7	1	15	2
	1				7*	2†				

\*5 emerged in patients susceptible to KM and OFX, 2 with initial OFX resistance.

†1 emerged in patients susceptible to KM and OFX, 1 with initial OFX resistance.

XDR-TB = extensively drug-resistant TB; MDR-TB = multidrug-resistant TB; TB = tuberculosis; OFX = ofloxacin; KM = kanamycin.

## RESULTS

In all, 104 patients (66 in the first cohort and 38 in the second) were treated for MDR-TB. Among these, 10 had initial OFX resistance, two had initial KM resistance, and one had both OFX and KM resistance (XDR-TB). Of the 12 patients with pre-XDR-TB (OFL/KM resistance), five were cured, three died, one

defaulted and three failed to respond to treatment, with emergence of XDR-TB. In addition, six of 91 patients who had initially OFX- and KM-susceptible organisms developed XDR-TB. We thus identified 10 XDR-TB patients from the two cohorts (Table 1).

The demographic profile of the patients, the treatment regimens used and the current status is given in Table 2. All the patients were human immunodeficiency

**Table 2** Profile of XDR-TB patients

No.	Age	Sex	Weight at diagnosis, kg	DST at start of MDR-TB treatment	Emergence of XDR-TB	Month/year XDR-TB diagnosis treatment started	Drugs received after diagnosis of XDR-TB	Status	Survival after XDR-TB diagnosis, months	Comorbidity
1	38	M	40	HR, OFX	OFX: initial KM: 4 months	<u>3/2001</u> 6/2001	AMK, CS, ETH, PAS, H600	Died	15	Hansen's disease
2	38	M	47	SHR	KM: 3 months OFX: 6 months	<u>12/2001</u> Died	Died before treatment could be initiated	Died	4	Diabetes mellitus
3	39	M	48.5	SHRE, KM, OFX, ETH	Pre-treatment XDR-TB	<u>12/2001</u> Initial default	Defaulted before treatment could be initiated	Initial default	18	Nil
4	49	M	56	HRE, ETH	KM: 4 months OFX: 25 months	<u>2/2005</u> 5/2006	OFX, EMB, CS, PAS, PZA, AMK, AUG, MGYL, CLO, MFX Surgical resection	Responding to treatment after surgery (smear- and culture-negative for 14 months); still on treatment	58	Nil
5	49	F	41	SHRE, OFX	OFX: initial KM: 7 months	<u>9/2003</u> Initial default	Defaulted before treatment could be initiated	Initial default	11	Nil
6	39	F	54	SHR	KM: 10 months OFX: 18 months	<u>6/2005</u> 4/2006	EMB, PZA, CS, PAS, GFX, AMK, AUG, CLM, ETH, INH, CFZ, MGYL	On treatment, culture-positive	54	Diabetes mellitus
7	25	M	40	SHR	KM: 4 months OFX: 9 months	<u>8/2005</u> 8/2006	AMK, AUG, CLM, H600, ETH, EMB, PAS, PZA	Defaulted from treatment	28	Nil
8	46	M	39	SHR, ETH	OFX: 9 months KM: 11 months	<u>2/2008</u> 9/2008	MFX, H600, EMB, CS, PAS, AUG	On treatment, culture-positive	22	Nil
9	32	F	29	SHR	KM: 3 months OFX: 55 months	<u>7/2008</u> 5/2009	AMK, MFX, AUC, CFZ, PZA, H600	On treatment, culture-positive	17	Nil
10	31	F	26	SHRE, OFX ETH	OFX: initial KM: 7 months	<u>1/2008</u> 9/2008	CPM, MFX, CS, PZA, EMB, PAS, AUG, CFZ, H600	Died	21	Nil

XDR-TB = extensively drug-resistant tuberculosis; DST = drug susceptibility testing; MDR-TB = multidrug-resistant tuberculosis; H = isoniazid; R = rifampicin; OFX = ofloxacin; KM = kanamycin; AMK = amikacin; CS = cycloserine; ETH = ethionamide; PAS = para-aminosalicylic acid; S = streptomycin; E, EMB = ethambutol; PZA = pyrazinamide; AUG = augmentin (amoxicillin + clavulanic acid); MGYL = metrogyl; CFZ = clofazimine; MFX = moxifloxacin; GFX = gatifloxacin; CLM = clarithromycin; CPM = capreomycin.

virus negative, two had diabetes mellitus and one had polyneuritic Hansen's disease. Six patients were male, with a median age of 40 years and a median weight of 43.2 kg. The chest radiographs of these patients showed bilateral parenchymal lesions involving 4–6 zones, and four had cavitory lesions.

Among the 10 XDR-TB patients, treatment could not be initiated in three, as one died due to massive haemoptysis and two defaulted. The remaining seven patients were treated with individually tailored regimens based on DST. One patient underwent a pulmonary lobectomy and became bacteriologically negative at the end of the first month of surgery. During treatment, one patient defaulted and two died due to respiratory failure. The remaining three patients are still bacteriologically positive and continue on treatment. All patients experienced mild to moderate adverse drug reactions, and the offending drug was either temporarily withheld or discontinued.

## DISCUSSION

We reported the first case of XDR-TB in a field setting in India in 2007.<sup>2</sup> Hospital-based studies published in India showed that the prevalence of XDR-TB varied between 2.4% and 33.3%,<sup>3</sup> with the highest rates observed in patients with full-blown acquired immune-deficiency syndrome.<sup>5</sup>

Published studies show that patients with FQ resistance are at risk of developing XDR-TB during treatment with SLDs, a risk that may increase if these drugs are administered outside the setting of a structured treatment programme.<sup>6</sup> However, we observed that XDR-TB occurs irrespective of FQ resistance, although the rate of emergence was higher among patients with FQ resistance. Further studies are required in a larger MDR-TB population to identify risk factors for the emergence of XDR-TB.

The first cohort was prior to the implementation of DOTS-Plus guidelines, and KM was given thrice weekly. Patients in the second cohort were treated as per the DOTS-Plus guidelines, with daily KM injections. Drug dosages were determined according to weight bands. It was observed that respectively eight (12%) and two (5%) cases in the first and second cohorts had XDR-TB. The lower rate of emergence of resistance in the second cohort could be attributed to the higher strength of the drugs used. The second cohort also had a shorter duration of follow-up.

This report describes the experience of the centre in treating cases who emerged as XDR-TB among a selected group of MDR-TB patients over a period of 10 years even before a definition for XDR-TB was available. The poor treatment outcomes observed warrant an early diagnosis of XDR-TB, prompt initiation of treatment, assured adherence and availabil-

ity of newer drugs such as later generation FQs and linezolid. One of the patients successfully underwent lobectomy; other published reports show that resectional lung surgery is associated with an initial favourable outcome and increased long-term survival in XDR-TB patients.<sup>7</sup>

The limitations of the results include the small number of cases, from two different patient cohort groups that were managed by a TB research centre and not under programme conditions.

## CONCLUSION

Although our experience with XDR-TB has not been encouraging, the lessons learnt are that there is a need to develop rapid methods for culture and DST against SLDs, to ensure the availability of quality-assured drugs and to devise appropriate guidelines for the management of XDR-TB.

## Acknowledgements

The authors are grateful to the Director General of the Indian Council of Medical Research for his encouragement and support. They thank V Kumaraswami, Director-in-Charge, R Ramachandran and T S Devi, former Deputy Director Senior Grade of Tuberculosis Research Centre (TRC) for their valuable comments; the Tamil Nadu State TB Officer and Programme Managers and staff of Tiruvallur District for their cooperation; TRC staff, particularly the Bacteriology, Clinic and Biochemistry divisions, for their support in patient management; and the patients for their cooperation and participation.

This study was supported in part by the World Health Organization, with financial assistance provided by the United States Agency for International Development under the Model DOTS Project.

## References

- 1 World Health Organization. Multidrug and extensively drug-resistant TB. 2010 Global report on surveillance and response. WHO/HTM/TB/2010.3. Geneva, Switzerland: WHO, 2010.
- 2 Thomas A, Ramachandran R, Rehaman F, et al. Management of multidrug resistance tuberculosis in the field: Tuberculosis Research Centre experience. *Indian J Tuberc* 2007; 54: 117–124.
- 3 Sharma S K, George N, Kadiravan T, Saha P K, Mishra H K, Hanif M. Prevalence of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: a retrospective hospital-based study. *Ind J Med Res* 2009; 130: 392–395.
- 4 Ministry of Health & Family Welfare. Revised National Tuberculosis Control Programme: DOTS-plus guidelines, November 2009. New Delhi, India: Central TB Division, Ministry of Health & Family Welfare, 2009.
- 5 Singh S, Sankar M M, Gopinath K. High rate of extensively drug-resistant tuberculosis in Indian AIDS patients. *AIDS* 2007; 21: 2345–2347.
- 6 Milambo C K, Warren R M, Poswa X, Victor T C, Duse A G, Marais E. Genotypic diversity of extensively drug-resistant tuberculosis (XDR-TB) in South Africa. *Int J Tuberc Lung Dis* 2008; 12: 99–104.
- 7 Chan E D, Laurel V, Strand M J, et al. Treatment and outcome analysis of 205 patients with multi drug resistant tuberculosis. *Am J Respir Crit Care Med* 2004; 169: 1103–1109.

## R É S U M É

On a identifié 10 patients atteints d'une tuberculose à germes ultrarésistants (TB-XDR) parmi 104 patients atteints d'une tuberculose à germes multirésistants (TB-MDR) et séronégatifs pour le virus de l'immunodéficience humaine en traitement au Tuberculosis Research Centre à Chennai, dans deux cohortes différentes entre 1999–2003 et 2006–2007. Ils ont été pris en charge et soumis à des régimes de traitement individualisés. Au moment du diagnostic de TB-MDR, la TB-XDR existait

chez un patient et une résistance initiale à l'ofloxacine chez trois patients. Chez un patient qui a bénéficié d'une lobectomie en plus de la chimiothérapie, l'examen bactériologique est devenu négatif, trois patients sont décédés, trois ont abandonné et les trois dont l'examen bactériologique reste positif sont toujours sous traitement. Bien qu'ils reposent sur un petit nombre de patients, nos résultats ne sont pas encourageants.

## R E S U M E N

En el centro de investigación de Chennai, se detectaron 10 pacientes con tuberculosis extremadamente drogoresistente (TB-XDR) en los 104 pacientes negativos para el virus de la inmunodeficiencia humana con tuberculosis multidrogoresistente (TB-MDR) tratados en este centro en dos cohortes diferentes del 1999 al 2003 y del 2006 al 2007. Estos pacientes recibieron pautas terapéuticas individualizadas. En el momento del diagnóstico de la TB-MDR, un paciente presentó TB-

XDR y tres exhibieron resistencia inicial a ofloxacino. Un paciente en quien se practicó una lobectomía además del tratamiento antituberculoso negativizó el esputo, tres pacientes fallecieron, hubo tres abandonos y los tres pacientes restantes, que siguen siendo bacteriológicamente positivos, continúan todavía el tratamiento. Si bien es cierto que el estudio se basa en una muestra pequeña, los resultados no son muy estimulantes.