Management of emerging multidrug-resistant tuberculosis in a low-prevalence setting

G. Catho[1,2], S. Couraud[3], S. Grard[1], A. Bouaziz[1], A. Sénéchal[1], F. Valour[1], T. Perpoint[1], E. Braun[1], F. Biron[1], T. Ferry[1,4], C. Chidiac[1], N. Freymond[3], E. Perrot[3], P.-J. Souquet[3], J.-M. Maury[5], F. Tronc[5], N. Veziris[6,7], G. Lina[4,8], O. Dumitrescu[4,8] and F. Ader[1,4], on behalf of the Lyon TB Study Group

1) *Service de Maladies Infectieuses et Tropicales, Hôpital de la Croix-Rousse, Hospices Civils de Lyon,* 2) *Service de Pneumologie et Allergologie Pédiatriques, Hôpital Femme-Mère-Enfant, Hospices Civils de Lyon, Bron,* 3) *Service de Pneumologie et Oncologie Thoracique, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite,* 4) *Inserm U1111 CIRI, Université Claude Bernard Lyon I, Lyon,* 5) *Departement de Chirurgie Thoracique, Hôpital Louis Pradel, Hospices Civils de Lyon, Bron,* 6) *AP-HP, Hôpital Pitié-Salpêtrière, Laboratoire de Bactériologie-Hygiène, Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux,* 7) *UPMC, INSERM, Centre d'Immunologie et des Maladies Infectieuses, E13, Paris, and* 8) *Laboratoire de Microbiologie, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France*

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Corresponding author: F. Ader, Service de Maladies Infectieuses et Tropicales, Hôpital de la Croix-Rousse, 103 Grande-Rue de la Croix-Rousse, 69317 Lyon cedex 04, France
E-mail: florence.ader@chu-lyon.fr
O. Dumitrescu and F. Ader contributed equally to this work
Lyon TB study group: F. Ader, F. Biron, A. Boibieux, A. Bouaziz, K. Bouledrak, E. Braun, G. Carret, G. Catho, N. Charhon, C. Chidiac, W. Chumbi-Flores, S. Couraud, G. Devouassoux, O. Dumitrescu, S. Ernesto, T. Ferry, D. Floret, N. Freymond, S. Gardes, S. Gerbier-Colomban, Y. Gillet, S. Goutelle, J. Grando, R. Grima, L. Hees, J. Karsenty, L. Kiakouama-Maleka, G. Lina, J. M. Maury, M. H. Metzger, P. Miailhes, L. Moreau, P. Nesme, T. Perpoint, E. Perrot, D. Peyramond, A. G. Ranc, R. Reix, A. S. Renaud-Baron, A. Senechal, P. J. Souquet, H. van Thai, F. Tronc, F. Valour and P. Vanhems

Abstract

Multidrug-resistant (MDR) tuberculosis (TB) is an emerging concern in communities with a low TB prevalence and a high standard of public health. Twenty-three consecutive adult MDR TB patients who were treated at our institution between 2007 and 2013 were reviewed for demographic characteristics and anti-TB treatment management, which included surgical procedures and long-term patient follow-up. This report of our experience emphasizes the need for an individualized approach as MDR TB brings mycobacterial disease management to a higher level of expertise, and for a balance to be found between international current guidelines and patient-tailored treatment strategies.

Keywords: Bedaquiline, MDR TB surgery, multidrug-resistant tuberculosis, *Mycobacterium tuberculosis*, negative-pressure ventilation room

Introduction

The emergence of multidrug-resistant (MDR) tuberculosis (TB) is a major concern. In 2014, MDR TB represented 5% of all TB cases [1]. Eastern European and Central Asian countries have the highest levels of MDR TB (35% of new cases and 75% of previously TB treated cases, respectively) [1]. Reports of patients with extensive drug-resistant TB are regularly referred to [2]. The MDR TB cure rate ranges from 44% to 83%, and patients with MDR TB have a higher death rate (10–14%) than those with susceptible TB [3]. Although France is among the western Europe countries with the lowest prevalence of MDR TB, its incidence has dramatically increased [4]. Assessing the strengths and weaknesses of our institutional practices is of critical importance to optimally confront this growing challenge.

Methods

We performed a retrospective analysis of all consecutively documented MDR TB adult cases patients who were treated at our institution between 2007 and 2013. A standardized template survey adapted from Sotgiu et al. [5], covering key TB items, was used to collect patient data, which included socio-

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demographic characteristics, clinical presentation, phenotypic drug susceptibility testing (DST) for all anti-TB drugs [6], strain genotyping as previously described [7,8], drug efficacy and tolerance, treatment outcome, surgical procedure, and long-term patient follow-up.

Results and discussion

Twenty-three patients with documented MDR TB were included. The male/female sex ratio was 2.8, and the mean age was 32 years. Twenty-one (91%) patients were foreign-born (2/3 from eastern Europe or Central Asia). Eighteen (78%) patients had not mastered any elementary language skill of the host country, and two-thirds of them received shelter from homeless public facilities. All patients but one (lymph node TB) had pulmonary MDR TB with clinical presentations of chronic cough (72%), weight loss (64%), fever (36%), and haemoptysis (28%). Four (17%) patients had hepatitis C virus or hepatitis B virus co-infection, and none had human immunodeficiency virus co-infection. Regarding TB medical history, eight (35%) patients had received prior curative anti-TB treatment, with unknown combinations for six (75%) of the patients.

Sixteen (70%) strains belonged to the East Asian Beijing genotype, and the Beijing genotype accounted for 7–11% in the susceptible TB cohort during the same period [9]. Studies suggest selective advantages of the Beijing genotype over other lineages, more likely to induce cavitary disease and a high sputum mycobacterial load [10,11].

Regarding DST, high resistance levels were observed for ethionamide, ethambutol, pyrazinamide, and cycloserine (78%, 70%, 56%, and 30%, respectively), resulting in drug interruption upon DST results. The resistance levels for amikacin, the later-generation fluoroquinolones moxifloxacin and levofloxacin, *p*-aminosalicylic acid and linezolid were <20% or null. The antibiotic regimen choices and completion followed the WHO guidelines [12]. The median treatment duration needed to obtain negative sputum conversion was 50.5 ± 35.8 days. Amikacin and fluoroquinolones were used in 87% and 91% of the cases, respectively (Table 1). The amikacin mean treatment duration, which barely exceeded 3 months, was the second shortest of all anti-TB drugs. Particular attention was given to amikacin-related hearing loss for incoming migrants who were in the process of learning a new language. Of 20 amikacin-treated patients, six (30%) developed audiogram-confirmed hearing loss (>20-dB loss at any tested frequency) that required drug interruption (Table 2) [13]. In the case of moderate renal function impairment, the dose adjustment was tested (increasing the dose interval to 48 h or lowering the daily dose from 15 to 10 mg/kg/day), which allowed three patients to receive further treatment. Overall, only three patients achieved amikacin maintenance during the entire 8-month intensive phase (Fig. 1). *p*-Aminosalicylic acid and linezolid were used in 83% and 78% of the cases, respectively (Table 1). Of 19 *p*-aminosalicylic acid-treated patients, nine (47%) developed nausea and vomiting, requiring drug interruption for eight patients (Table 2). A high ethionamide resistance rate (78%) resulted in a shift to linezolid, because recent studies have confirmed that linezolid is an effective MDR TB drug [14]. For the 18 linezolid-treated patients, lowering the daily dose from 1200 mg to 600 mg undoubtedly improved long-term linezolid tolerability, despite two (11%) interruptions for cytopenia and

TABLE 1. Use of individual anti-tuberculosis (TB) drugs with respect to timing and optimization of use, cause of interruption and mean treatment duration in 23 multidrug-resistant TB patients

	Group I		Group II	Group III	Group IV			Group V		
Drug use	EMB	PZA	AMK	FQ	ETO	CS	PAS	LNZ	BDQ	CBP + AMX + CLAV
Overall, *n* (%)	12 (48)	11 (44)	20 (87)	21 (91)	12 (48)	15 (65)	19 (83)	18 (78)	10 (43)	2 (8)
Part of the first combination, *n* (%)	12 (100)	11 (100)	18 (90)	21 (100)	11 (92)	13 (87)	15 (79)	12 (67)	2 (20)	1 (50)
Part of the second combination, *n* (%)	–	–	1 (5)	–	1 (8)	2 (13)	1 (5)	4 (22)	6 (60)	1 (50)
Part of the third combination, *n* (%)	–	–	1 (5)	–	–	1 (7)	3 (16)	2 (11)	2 (20)	–
Median number of drug changes (range)	3.24 (2–6)									
Resistance-related drug interruption, *n* (%)	6 (50)	2 (18)	1 (5)	2 (9,5)	6 (50)	2 (13)	1 (5)	0 (0)	0 (0)	1 (50)
Side effect-related drug interruption, *n* (%)	0 (0)	1 (9)	7 (35)	0 (0)	1 (8)	1 (7)	9 (47)	8 (44,5)	0 (0)	0 (0)
Drug use mean duration in days (range)	369 (15–671)	470 (76–671)	113 (30–244)	372 (33–701)	296 (15–671)	299 (21–701)	207 (9–518)	229 (30–701)	181 (170–186)	100

AMK, amikacin; AMX + CLAV, amoxycillin–clavulanate; BDQ, bedaquiline; CBP, carbapenem (imipenem or meropenem); CS, cycloserin; EMB, ethambutol; ETO, ethionamide; FQ, later-generation fluoroquinolones (moxifloxacin or levofloxacin); LNZ, linezolid; PAS, *p*-aminosalicylic acid; PZA, pyrazinamide.

TABLE 2. Drug-related adverse events and subsequent requirement for dosage adjustment or drug interruption in 23 multidrug-resistant tuberculosis patients

Adverse events	*n*	Drug-related	Event requiring dosage adjustment, *n* (%)	Event requiring drug interruption for >5 days, *n* (%)
Hearing loss	6	AMK	—	6 (100)
Nephrotoxicity	4	AMK	3 (75)	1 (25)
Gastritis, nausea, vomiting	9	PAS	—	8 (89)
Psychiatric effects	2	CS	1 (50)	1 (50)
Hypothyroidism	3	ETO, PAS, CS	—	1 (33)
Joint/musculoskeletal pain	5	FQ	—	—
Neuropathy (peripheral and optic)	7	LNZ	—	6 (86)
Cytopenia (anaemia, thrombopenia)	8	LNZ	6 (75)	2 (25)
Hepatitis	3	PZA	—	1 (33)

AMK, amikacin; CS, cycloserin; ETO, ethionamide; FQ, later-generation fluoroquinolones (moxifloxacin or levofloxacin); LNZ, linezolid; PAS, *p*-aminosalicylic acid; PZA, pyrazinamide.

six (33%) mandatory interruptions for peripheral neuropathy (Table 2). The novelty was the use of a 24-week regimen of the diarylquinoline anti-TB drug bedaquiline for ten (43%) patients. In placebo-controlled studies, adding bedaquiline to standard therapy for MDR TB reduced the time to conversion and increased the proportion of patients with negative sputum conversion [15,16]. Minor clinically relevant side effects, primarily nausea, were reported. No changes in heart rate or electrocardiographic QRS or PR intervals were observed when bedaquiline was combined with fluoroquinolones. Although caution is recommended until upcoming phase III trial results are available, bedaquiline is expected to replace the most toxic drugs and to contribute to shortening MDR TB treatment [17].

Sixteen (70%) patients had cavitary lesions involving one or more pulmonary lobes. Previous studies support an improved outcome when both surgical resection and an optimized drug combination are used [18]. The surgical resection of cavitary lesions or destroyed lungs was individually considered for seven patients upon negative sputum conversion that was deemed to fail medical treatment (complex resistance patterns and/or the extent of the disease). Six patients agreed to surgery. The mean treatment duration before surgery was 6.6 months (range, 3–15 months), which was a rather short delay considering that our primary goal was a decrease in mycobacterial burden to improve the treatment outcome. Immediate postoperative complications were prolonged air leakage through bronchial sutures and mild bleeding for two patients.

Previously published consensus definitions for treatment outcome were used [19]. In our series, the median duration of follow-up was 30 ± 8.2 months. Eighteen (78%) patients completed the treatment, with no attributable related mortality and relapse-free cure thus far. Three patients defaulted, and two patients remain in the continuation phase, with three active anti-TB drugs (Fig. 1). Notably, only nine (39%) patients could be isolated in the single negative-pressure ventilation room of our facility from the time of admission until sputum conversion.

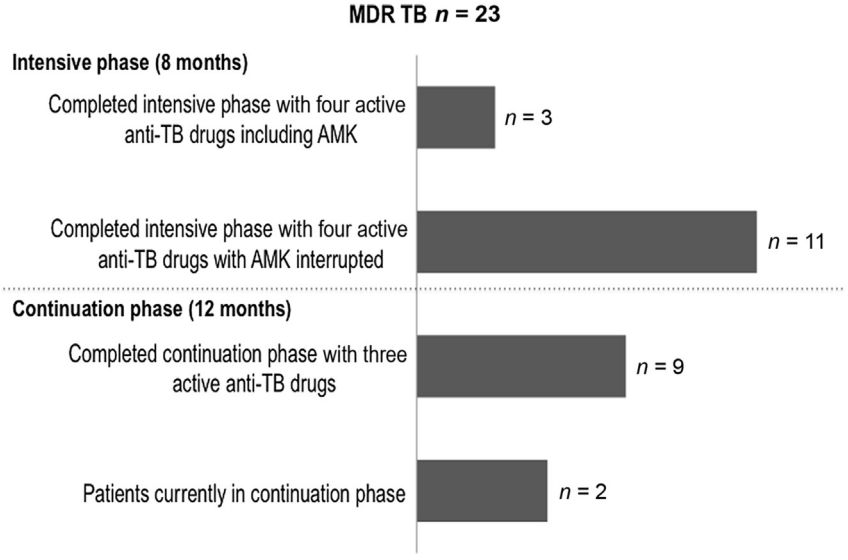

FIG. 1. Summary of multidrug-resistant (MDR) tuberculosis (TB) patients who achieved intensive and continuation phases with the recommended number of drugs, and the current status of ongoing treatments (the intensive phase lasted for 8 months, and the continuation phase lasted for 12 months). AMK, amikacin.

MDR TB treatment faces the difficulties of individually tailoring the most appropriate treatment strategy and combining efficacy, safety, and tolerability.

Transparency declaration

The authors declare that they have no conflicts of interest.

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