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Treating children for drug-resistant tuberculosis in Tajikistan with Group 5 medications

A. Swaminathan,* P. du Cros,† J. A. Seddon,†‡ S. Quinnell,* O. I. Bobokhojaev,§ Z. Dusmatova,* J. Achar†

***Médecins Sans Frontières (MSF), Dushanbe, Tajikistan; †Manson Unit, MSF, London, ‡Imperial College London, London, UK; §National Tuberculosis Programme, Ministry of Health and Social Protection of the Republic of Tajikistan, Dushanbe, Tajikistan**

SUMMARY

BACKGROUND: Management of extensively drug-resistant tuberculosis (XDR-TB) and pre-XDR-TB is challenging, as effective drugs are lacking. Group 5 antituberculosis drugs have an unclear role in the treatment of drug-resistant TB, and in children the efficacy, safety and effects of long-term use are not well described. We present clinical outcomes and adverse effects of a cohort of children with XDR-TB or pre-XDR-TB treated with Group 5 drugs in Tajikistan.

METHODS: We conducted a retrospective analysis of eight children treated with one or more of the Group 5 drugs available under the Tajikistan National TB Programme—linezolid, amoxicillin-clavulanate, clofazimine and clarithromycin—given in combination with first- and second-line drugs. Time to sputum culture conversion, clinical outcomes and adverse effects were evaluated.

RESULTS: Two children were cured, one completed treatment, four achieved favourable interim outcomes and one died. Adverse effects attributable to linezolid that required drug cessation occurred in one child; adverse effects of the other Group 5 drugs were insignificant or absent, requiring no regimen changes.

CONCLUSION: Group 5 drugs can contribute to effective regimens in children with XDR and pre-XDR-TB. With proper monitoring and aggressive management of adverse effects, their safety profile might be acceptable, even in long-term use.

KEY WORDS: linezolid; clofazimine; amoxicillin-clavulanate; neuropathy; MDR-TB

THE EMERGENCE AND SPREAD of multidrug-resistant tuberculosis (MDR-TB, defined as TB resistant to at least isoniazid [INH] and rifampicin [RMP]) threatens progress in global TB control.[1] Up to 20% of TB cases occur in children, and annually more than 30 000 develop MDR-TB.[2] Once on treatment, up to 82% of children with MDR-TB achieve favourable outcomes.[3]

Patients with strains of MDR-TB resistant to second-line drugs, in particular the fluoroquinolones (FQs), have worse outcomes, even with access to Group 5 drugs.[4] Among all new and retreatment TB cases, the proportion of MDR-TB and extensively drug-resistant TB (XDR-TB, defined as MDR-TB with additional resistance to a FQ and a second-line injectable drug) is highest in the World Health Organization (WHO) European Region.[5] In Tajikistan, the proportion of MDR-TB is 13% among new patients and 56% in retreatment cases.[6] In the Médecins Sans Frontières (MSF)/Ministry of Health and Social Protection of the Republic of Tajikistan (MoH) TB Programme, children with XDR-TB or pre-XDR-TB (defined as MDR-TB with resistance to either an injectable or an FQ) receive regimens that include one or more of the four available Group 5 drugs: linezolid (LZD), clofazimine (CFZ), amoxicillin/clavulanate (AMX/CLV) and clarithromycin (CLM). Although Group 5 TB drugs, classified by the WHO as having 'unclear efficacy or unclear role in drug-resistant TB treatment', are increasingly being used for the management of MDR-TB with injectable and/or FQ resistance, efficacy and safety data in children are limited. We present the clinical outcomes and adverse effects of a cohort of children with XDR-TB or pre-XDR-TB treated with Group 5 drugs in Tajikistan.

METHODS

We conducted a retrospective review of all patients aged <18 years admitted to the MSF/MoH programme between October 2012 and October 2014 with XDR-TB or pre-XDR-TB and started on regimens that included one or more of the Group 5

Correspondence to: Aravind Swaminathan, Department of Paediatrics, Saveetha Medical College, Thandalam, Kancheepuram, Tamil Nadu, India. e-mail: draravind08@gmail.com
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drugs. Programme data were analysed to the end of May 2015. Interim clinical and microbiological outcomes, final treatment outcomes and adverse effects of Group 5 drugs were assessed.

Diagnosis was based on drug susceptibility testing (DST) results (National Reference Laboratory, with quality control by the Supranational Reference Laboratory, Gauting, Germany). In case of negative or inconclusive sputum samples or DST results, DST results of close household source cases and the child's previous treatment history helped determine the treatment regimen. DST against all drugs except pyrazinamide (PZA) was performed using standard culture on Löwenstein-Jensen medium. First-line drugs were assessed using the proportion method with the following concentrations: streptomycin 4 μg/ml, INH 0.2 μg/ml, RMP 40 μg/ml and ethambutol 2 μg/ml. Second-line drugs were assessed by absolute concentration: ofloxacin 2 μg/ml, capreomycin 40 μg/ml, kanamycin 30 μg/ml, and amikacin 30 μg/ml. DST against PZA was performed using BACTEC MGIT™ 960™ (BD, Sparks, MD, USA) (100 mg/l).

Patients were managed according to MSF-PIH (Partners in Health) protocols[7] and other international guidelines,[8] with consultation from international experts and approval by the local official body (the *consilium*) for quality assurance in anti-tuberculosis treatment. Regimens included $\geqslant$4 likely effective drugs, chosen according to availability and registration. LZD was administered at 10 mg/kg/dose twice daily for children $\leqslant$30 kg and 600 mg once daily for those >30 kg. The dose was reduced at 4 months after sputum culture conversion if other effective drugs were available or in the case of adverse events. CFZ was given at 2–3 mg/kg/day for patients $\leqslant$30 kg; those >30 kg received 200 mg/day for 6 weeks, followed by 100 mg/day. AMX/CLV was given at 80 mg/kg/day (up to 3000 mg/day) in two divided doses. One patient received CLM at 1000 mg/day.

Treatment was directly observed 6 days/week. Patients were followed up by a TB specialist at least monthly. Sputum smear microscopy and culture were performed monthly during the intensive phase; DST was performed every 2 months from month 4 of treatment if cultures were positive. During the continuation phase, sputum smear microscopy, culture and DST were performed every 3 months. Patients on LZD had complete blood counts (weekly in the first month and then monthly), were questioned on vision disturbances and undertook Ishihara tests (monthly in children who could cooperate and communicate). Therapeutic drug monitoring was not undertaken. All data were entered into a standard database (Koch 6, MSF, Paris, France).

This retrospective review of routine programme data met the MSF Ethics Review Board criteria for exemption from ethics review.

RESULTS

Patient characteristics and regimens

Eight children (six girls) received treatment for XDR-TB or pre-XDR-TB. Clinical profiles are summarised in the Table. At analysis, the children had received treatment for a median of 20.5 months. Of the 8 children, 6 had pulmonary TB (PTB) and 2 had extrapulmonary TB (EPTB); all were human immunodeficiency virus negative. One had co-existent type 1 diabetes mellitus (DM). Three had not received prior treatment with anti-tuberculosis drugs, four had previously been treated with Group 1 first-line anti-tuberculosis drugs, and one had previously undergone treatment for MDR-TB. Three had XDR-TB, two had MDR-TB with resistance to FQs, one had MDR-TB with resistance to a second-line injectable and two had negative cultures but close household contact with an XDR-TB patient and a pre-XDR-TB patient (injectable resistance), respectively.

The children received a median of seven drugs (range 6–8) during the intensive phase. Group 5 drugs were included in the initial regimen for four children; for four others they were added after a median of 5 months, either on receipt of second-line DST results or if these suggested the evolution of pre-XDR-TB or XDR-TB. One child received four Group 5 drugs (LZD, CFZ, AMX/CLV and CLM, with dose adjustment of CLM due to likely interaction between LZD and CLM); four received LZD, AMX/CLV and CFZ; two received AMX/CLV and CFZ; and one received only LZD as part of the regimen.

Outcomes

Three children achieved a favourable final outcome (cured or treatment completed), four are still in the continuation phase, and one (with PTB) died in the intensive phase after failing to respond to 5 months of treatment. Among the six children with PTB, five (including the two declared cured) achieved favourable interim outcomes (sputum smear and culture conversion): one before Group 5 drugs were added to the regimen, and four at a median of 2.5 months after the addition of the drugs. Among the two children with EPTB, one completed treatment, while the other had good clinical response and is in the continuation phase. None failed treatment or were lost to follow-up.

Adverse effects

Six children received LZD for a median of 15 months (range 12–21). Haematological and neurological abnormalities were noted in one patient (with co-existent type 1 DM) who had transient thrombocytopaenia at month 6 and painful peripheral neuropathy at month 8 that required cessation of LZD. Symptoms of peripheral neuropathy resolved following cessation.

Seven children received CFZ for a median of 20

Table Clinical profiles of the eight children who received treatment for XDR-TB or pre-XDR-TB

No	Age years	Sex	Previous anti-tuberculosis treatment *	Contact history	Symptom duration before sample was taken	Type of diagnostic sample used	Chest X ray findings
1	16	F	Category 1 and 2	No	3 months	Sputum	Infiltrates: right lung >1 lobe, left lung >1 lobe
2	5	F	Category 1	Yes	1 month	Lymph node	Normal
3	17	F	Category 1	No	6 months	Sputum	Cavities in both lungs; infiltrates: right lung >1 lobe, left lung >1 lobe; left sided pleural effusion
4	14	F	Category 1, Category 4 (MDR-TB regimen) for 7 months	Yes	7 months	Sputum	Cavities in both lungs; infiltrate: right lung >1 lobe
5	12	F	No	Yes	1 month	Based on contact's DST	Infiltrate: left lung (1 lobe); nodules: left lung (1 lobe)
6	15	M	No	Yes	2 weeks	Sputum	Cavity: left lung (1 lobe). Infiltrate: left lung >1 lobe
7	15	F	No	Yes	1 month	Sputum	Infiltrate: right lung (1 lobe), left lung >1 lobe
8	30 months	M	Category 1 (2 months)	Yes	15 days	Based on contact's DST	Pleuritis, pericarditis; left pleural effusion

* According to WHO classification: Category 1 = initial regimen with first-line drugs; Category 2 = retreatment regimen with first-line drugs; Category 4 = second-line treatment regimen.
XDR-TB = extensively drug-resistant tuberculosis; DST = drug susceptibility testing; F = female; H = isoniazid; R, RIF = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin; PTH = prothionamide; MFX = moxifloxacin; OFX = ofloxacin; KM = kanamycin; CPM = capreomycin; LZD = linezolid; AMX/CLV = amoxicillin/clavulanate; CFZ = clofazimine; CS = cycloserine; PAS = para-amino salicylic acid; AMK = amikacin; CLM = clarithromycin; MDR-TB = multidrug-resistant TB; MTB = *M. tuberculosis*; M = male; WHO = World Health Organization.

months (range 19–23). Two developed reddish brown discolouration of the skin in sun-exposed areas. Two developed ichthyosis in the legs after 4–6 months, which resolved spontaneously after 8–10 weeks, even while on CFZ. One had transient gastritis, possibly due to long-term CFZ. However, none of these side effects required dose reduction or stoppage.

Seven children received AMX/CLV for a median of 20 months (range 19–23). There were no major adverse effects attributable to this drug. One child received CLM for 20 months. No side effects were noted. The child also received LZD, the serum concentration of which is potentially increased by CLM-mediated inhibition of metabolism;[9] however, no adverse effects of LZD were noted.

DISCUSSION

Our results show that Group 5 anti-tuberculosis drugs, when used appropriately, appear safe and effective in the management of drug-resistant TB in children. Among the 8 children in our cohort, 2 were cured, 1 completed treatment, while 4 achieved favourable interim outcomes; only 1 child developed serious adverse effects (LZD). With few paediatric data available, our cohort analysis, which includes standard protocols for treatment, follow-up and data collection, is a useful addition to the literature.

Reports of adults treated with Group 5 anti-tuberculosis drugs have been encouraging.[10] Data on LZD use in 16 children (from seven different reports) show that all achieved sputum culture conversion, while 14 achieved a successful long-term outcome, often despite extensive disease, substantial drug resistance, prolonged culture positivity and previous failed second-line treatment.[11] Peripheral neuropathy was noted in four of these children, but resolved after dose reduction or discontinuation. A meta-analysis[12] noted a sputum culture conversion rate of 98% with LZD, with neuropathy and bone marrow suppression the most common adverse effects (respectively 36% and 28%), in addition to

Table (continued)

DST	Regimen	Adverse effect attributed to Group 5 drug	Interim outcome	Final outcome
HRZES, PTH, MFX, OFX, KM, CPM-resistant	LZD+MFX+AMX/CLV+CFZ+PTH+CS+PAS	None	Good clinical response; achieved sputum conversion	Cured following 25 months of treatment
HRZE, MFX, OFX, PTH-resistant; CM, KM-susceptible	Z+MFX+AMK+CS+CFZ +AMX/CLV+PAS	Transient gastritis (CFZ)	Good clinical response; lymph node enlargement completely regressed	Treatment completed following 24 months of treatment
HRZES, OFX, MFX, KM, AMK, CPM, PTH-resistant	LZD+MFX+Z+CS+AMX/CLV+CFZ+CLM	Ichthyosis (CFZ)	Clinical improvement present; sputum conversion achieved	Received 27 months of XDR-TB regimen Plan: 30 months in total
HRZES, MFX, OFX, KM, CPM, AMK PTH-resistant	Z+LZD+AMK+MFX+CS +AMX/CLV+CFZ	None	Poor clinical response; sputum conversion not achieved	Died after 5 months of treatment
Not available as culture was negative; the Xpert test showed MTB+ and RIF-resistant (DST of contact showed HRES, OFX, CPM-resistant; Z, KM AMK-susceptible)	Z+AMK+MFX+PTH+CS +AMX/CLV+CFZ+PAS	None	Good clinical response; sputum conversion achieved	Received 20 months of treatment Plan: 24 months in total
HRS, KM, AMK, CPM-resistant; ZE, OFX-susceptible	LZD+CPM+MFX+Z+PTH +AMX/CLV+CFZ+E	Ichthyosis and reddish skin discoloration (CFZ); thrombocytopenia and peripheral neuropathy (LZD stopped)	Good clinical response; sputum conversion achieved	Cured following 21 months of treatment
HRSE, OFX-resistant; KM, AMK CPM-susceptible	LZD+MFX+CM+Z+PTH +CS+CFZ+AMX/CLV	Reddish skin discolouration (CFZ)	Good clinical response; sputum conversion achieved	Received 19 months of treatment Plan: 24 months in total
Not available (extra-pulmonary) (DST of contact showed HRS, KM, AM, CM-resistant; E, OFX-susceptible)	LZD+CPM+LFX+PTH +CS+Z	None so far	Good clinical response (doing well following subtotal pericardiectomy)	Received 12 months of treatment Plan: 20–24 months in total.

gastrointestinal effects (diarrhoea, vomiting), myelosuppression and lactic acidosis. LZD has good tissue penetration,[13,14] and has been added to the WHO Essential Drugs List.[15]

Good outcomes have been reported for CFZ-based short-course regimens in adults.[16] A meta-analysis reported an overall success rate of 62% with CFZ-based regimens,[17] with gastrointestinal disturbances and skin pigmentation the most common adverse effects. In leprosy patients, long-term treatment with CFZ is well tolerated, rarely requiring discontinuation; however, the dosages are often lower than used in TB.[18,19] Gastrointestinal adverse effects in children have not been well reported. Case reports on two children with leprosy treated with CFZ describe severe haematemesis[18] and enteropathy.[20] AMX/CLV has demonstrated in vitro activity against MDR/XDR-TB.[21] Meropenem and CLV with LZD produced good results in a 14-year-old patient with XDR-TB.[22]

We encountered practical programmatic issues: the introduction, registration and licensing of new anti-tuberculosis drugs in Tajikistan; training needs; the establishment of monitoring facilities; limited laboratory resources for sputum culture and DST; and ensuring clear communication with patients and health care providers on the use of drugs of 'unclear efficacy'.

Our study has limitations. Regimens comprised Group 5 and second-line drugs that were likely to be effective and some drugs that might not have been effective or had previously been used for treatment (e.g., PZA). Multiple drugs were used in individualised regimens, hindering definitive attribution of outcomes and adverse effects to any particular drug or group. Only three children achieved successful outcomes. Follow-up is needed to monitor for relapse and to gain insight into the effectiveness of the regimens in reducing mycobacterial burden and replication, and achieving sterilisation. Finally, there was absence of microbiological confirmation in some patients (culture-negative PTB and TB pericarditis).

CONCLUSION

Group 5 anti-tuberculosis drugs, when used appropriately, appear safe and effective in the management of drug-resistant TB in children; however, evidence remains limited. Drug choices depend on the availability of the drugs and paediatric-friendly formula-

tions, efficacy, safety, comorbidities, drug-drug interactions and facilities for monitoring adverse effects. LZD and CFZ are being included in many of the ongoing treatment trials in adults—with or without the new agents bedaquiline, delamanid and Pa-824—and are likely to be highly important in treatment regimens in the future. As so little is known about their use in children, our cohort data are important. With the new agents increasingly being used for drug-resistant TB, there is a need for better evidence and guidance for the selection and use of these drugs in children, as no pharmacokinetic, formulations or safety data for any of these drugs in children are currently available. However, if or when these data become available, many TB programmes will not have access to these expensive drugs.

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RESUME

CONTEXTE : La prise en charge de la tuberculose ultrarésistante (TB-XDR) et de la pré- TB-XDR est un défi parce que les médicaments efficaces manquent. Les médicaments antituberculeux du Groupe 5 ont un rôle peu clair dans le traitement de la TB pharmacorésistante ; chez les enfants, l'efficacité, la sécurité et les effets de l'utilisation à long terme n'ont pas été bien décrits. Nous présentons l'évolution clinique et les effets secondaires dans une cohorte d'enfants atteints de TB-XDR ou de pré-TB-XDR traités avec des médicaments du Groupe 5 au Tadjikistan.

MÉTHODES : Nous avons réalisé une analyse rétrospective sur huit enfants traités avec un ou plusieurs médicaments du Groupe 5 disponibles auprès du Programme national TB du Tadjikistan (linezolide [LZD], amoxicilline-clavulanate, clofazimine et clarithromycine), qui ont été administrés en plus des médicaments de première et deuxième ligne. Le délai de conversion de la culture de crachats, l'évolution clinique et les effets secondaires ont été notés.

RÉSULTATS : Deux enfants ont guéri, un enfant a achevé son traitement, quatre enfants ont eu un bon résultat provisoire et un est décédé. Des effets secondaires attribuables au LZD qui ont nécessité l'arrêt du traitement sont survenus chez un enfant ; les effets secondaires des autres médicaments du Groupe 5 ont été insignifiants ou absents, ne nécessitant pas de modification du protocole.

CONCLUSION : Les médicaments du Groupe 5 peuvent contribuer à des protocoles efficaces chez les enfants atteints de TB-XDR et pré-TB-XDR. Avec un suivi approprié et une prise en charge vigoureuse des effets secondaires, leur profil de sécurité pourrait être acceptable, même en utilisation prolongée.

RESUMEN

MARCO DE REFERENCIA: La atención de la tuberculosis ultrarresistente (TB-XDR) y la TB pre-ultrarresistente (pre-TB-XDR) plantea grandes dificultades debido a la falta de medicamentos eficaces. La utilidad del Grupo 5 de los medicamentos antituberculosos en el tratamiento de la TB resistente no es clara y en los niños no se ha definido plenamente su eficacia, seguridad toxicológica y sus efectos con la administración a largo plazo. En el presente artículo se comunican los desenlaces clínicos y las reacciones adversas de una cohorte de niños con diagnóstico de TB-XDR o pre-TB-XDR que recibía tratamiento con medicamentos del Grupo 5 en Tayikistán.

MÉTODOS: Se llevó a cabo un análisis retrospectivo de ocho niños tratados con uno o varios de los medicamentos del Grupo 5 que están al alcance en el Programa Nacional contra la Tuberculosis de Tayikistán (linezolid, amoxicilina + ácido clavulánico, clofazimina y claritromicina), administrados en asociación con medicamentos de primera o segunda línea. Se evaluaron el lapso hasta la conversión del esputo, el desenlace clínico y las reacciones adversas.

RESULTADOS: Dos niños alcanzaron la curación, uno completó el tratamiento, cuatro obtuvieron desenlaces intermedios favorables y un niño murió. Un niño presentó reacciones adversas atribuibles al LZD que justificaron la interrupción de su administración; las reacciones adversas a los demás medicamentos del Grupo 5 fueron insignificantes o ausentes y no dieron lugar a modificaciones del régimen terapéutico.

CONCLUSIÓN: Los medicamentos del Grupo 5 pueden contribuir eficazmente al régimen terapéutico en los niños con TB-XDR y pre-TB-XDR. Con una supervisión adecuada aunada al tratamiento enérgico de las reacciones adversas, la seguridad toxicológica de estos medicamentos podría ser aceptable, incluso durante una administración a largo plazo.