



Compassionate Use of New Drugs in Children and Adolescents with Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: Early Experiences and Challenges

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Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges

To the Editor:

The World Health Organization (WHO) estimated that 480 000 new multidrug-resistant (MDR) tuberculosis (TB) cases occurred globally in 2014, with 190 000 deaths. Limited data are available on the burden of MDR-TB in children. A recent systematic review estimated that 32 000 children acquire MDR-TB annually; of these, very few are correctly diagnosed and provided with appropriate treatment [1].

Treatment of drug-resistant TB is long, expensive and associated with frequent adverse events [1–5]. In children, treatment is further complicated by limited data on appropriate dosing and safety, and a lack of child-friendly formulations. New anti-TB drugs are urgently needed to improve treatment tolerability and outcome, particularly for MDR-TB cases with additional second-line drug resistance, for whom identifying at least four active drugs is difficult with the current armamentarium of drugs [1, 4–11]. Two novel anti-TB drugs, delamanid [6, 8, 12] and bedaquiline [6, 7, 9, 10, 12], have received conditional approval for use in adults with MDR-TB. While the WHO interim guidance does not include a recommendation on their use in children due to lack of data, the Centers for Disease Control and Prevention guidelines state that bedaquiline use can be considered for children when treatment options are limited.

A number of paediatric clinical trials are ongoing or planned. The Otsuka 232 (phase 1, pharmacokinetics and safety to determine the appropriate dose for MDR-TB in children) and 233 (phase 2, 6-month safety, efficacy and pharmacokinetics trial in children with MDR-TB) trials of delamanid have begun recruitment. Preliminary pharmacokinetics and safety data in 6–17-year-old children from these trials have been presented, showing an excellent safety profile and leading to weight-based dosing recommendations for patients of 20–35 kg to receive half the adult dose (50 mg of delamanid twice daily) (presented in poster format (A-960) by J. Hafkin; Pharmacokinetics and safety of delamanid in paediatric MDR-TB patients, ages 6–17 years; San Diego, Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 2015). A follow-up study to confirm the long-term safety, tolerability and pharmacokinetics of delamanid in these age groups and younger children (0–5 years) is ongoing and data are not yet available (presented in poster format (EP-115-04) by J. Hafkin; Long-term safety, tolerability and pharmacokinetics of delamanid in paediatric MDR-TB patients, ages 12–17 years; Cape Town, The 46th Union World Conference on Lung Health, 2015). Neither the Janssen C21 trial of bedaquiline (phase 2, pharmacokinetics, tolerability and anti-mycobacterial activity in children with MDR-TB) nor the US National Institutes of Health International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network planned trial of bedaquiline pharmacokinetics and safety in HIV-infected and uninfected children, have yet begun enrolling.

The Janssen bedaquiline compassionate use programme excluded all subjects aged <18 years, while delamanid is available to children from 12 years of age, and recently from 6 years, through the Otsuka compassionate use programme. Each request for delamanid compassionate use submitted to Otsuka is reviewed by an independent panel of experts, to assess the appropriateness and safety of delamanid use before the drug is provided. The aim of this report is to share the initial experience and challenges of compassionate use of delamanid in children and adolescents at a global level. The information reported here was collected through the two bodies providing independent advice on the rational use of new drugs: the TB Consilium (www.tbconsilium.org) [8] and the endTB committee (Médecins Sans Frontières (MSF), Partners in Health, and Interactive Research and Development; www.endtb.org).

Between February 2014 and March 2016, Otsuka received 19 requests for delamanid compassionate use for paediatric patients aged <18 years. All requests were considered appropriate by both the external committees and Otsuka, and hence were enrolled in the delamanid compassionate use programme. Requests were received from Italy (n=1), South Africa (n=5), Georgia (MSF settings; n=4), India (n=5;

four from MSF settings), Namibia (n=1), Swaziland, Russia and Armenia (MSF settings; one case each). Data from patients are summarised in table 1.

The rationale for delamanid requests was mainly the limited treatment options due to extensive resistance pattern or poor response to second-line anti-TB treatment, although in one case it was for reinforcement of the treatment regimen in a patient with adverse events. The TB Consilium and endTB committee experts recommended the use of delamanid as the best treatment option in these patients.

All 19 paediatric cases enrolled in the delamanid compassionate use programme had bacteriologically confirmed pulmonary MDR- or extensively drug-resistant (XDR)-TB (two cases also had extrapulmonary TB). Drug susceptibility testing confirmed resistance to four to 15 anti-TB drugs. Only three patients (patients 5, 6 and 19 in table 1) were HIV positive.

Out of 19 enrolled patients, 16 (84%) have already started treatment with delamanid. The mean age at treatment initiation was 14.4 years (range 8–17 years). All cases received delamanid 100 mg twice daily (adult dosage), except one who received 50 mg twice daily due to a body weight of 22 kg. Of these, six patients have already completed 24 weeks of delamanid, while 10 are still receiving the delamanid.

All patients showed good tolerability to delamanid with no or mild adverse events, except one patient from India. This patient was receiving a combination of delamanid-capreomycin-ethionamide-cycloserine-clofazimine-imipenem-amoxicillin/clavulanate-pyrazinamide, and experienced severe vomiting, renal impairment and severe electrolyte disturbances (hypokalaemia and hypomagnesaemia) that led to QTcF (QT interval in the ECG corrected according to Fredericia formula) prolongation (>500 ms) requiring temporary delamanid discontinuation (albumin was normal). After management of vomiting and electrolyte imbalance correction, the patient was able to complete delamanid treatment without further QTcF prolongation.

As shown in table 1, the interim treatment response is good: 13 (81.2%) out of 16 were *Mycobacterium tuberculosis* culture-negative at the time of this report (three patients were recently started on delamanid, so the interim treatment responses are not yet available). Except for one patient who has successfully completed MDR-TB treatment, the remaining patients are continuing treatment and do not have final treatment outcomes yet.

The combination of delamanid and bedaquiline has been limited due to concerns regarding the QT prolongation effects of both drugs. However, there are initial experiences with their simultaneous use in adults (now also possible through compassionate use) [13, 14]. This combination could be considered in children in the absence of effective alternative treatment options [4, 5], under enhanced clinical monitoring [12–15].

Globally, there are very few children who have access to delamanid compared with the likely number who could benefit from it. Healthcare providers have described a number of challenges to the access of delamanid. The compassionate use mechanism, despite efforts to facilitate quick access, is a long, multistep and time-demanding process (request, permission for importation/use, informed consent, health staff training on the compassionate use protocol, reporting requirements and importation). This can result in substantial delays in treatment initiation, which could adversely affect treatment outcome. In our study, the median delay between process initiation and delamanid initiation was 73.5 days (range 14–153 days). The recent announcement that delamanid is accessible through the Global Drug Facility for USD 1700 per treatment is an important step forward in increasing international access, avoiding the need for a compassionate use mechanism. However, countries may still face other barriers, such as lack of appropriate tools (clinical guidelines, appropriate training and national implementation plans), pharmacovigilance reporting requirements (which, although essential, are a new challenge for providers and programmes), and, lastly, budgets to cover the costs of these drugs. All are required to ensure rational use of delamanid in adult and paediatric patients.

In addition, the lack of inclusion of children in bedaquiline trials to date is not acceptable and contributes to the current situation of very limited access to this drug among children.

Wider availability of both drugs for children, including those with clinical TB and contact with a known MDR/XDR-TB source case, is urgently needed, as is the proactive inclusion of children and adolescents in trials of novel TB drugs [16].

Case-by-case evaluation from independent bodies like the TB Consilium and endTB committee is a valuable support to clinicians and programmes in the use of the new drugs in children, particularly where the clinical cases are complex and in the absence of formal guidance for their paediatric use. The use of these services could contribute to an increase in the appropriate use of new drugs among children and adolescents in need.

TABLE 1 Paediatric cases enrolled in Otsuka delamanid compassionate use programme, from February 2014 to March 2016

Patient	Country of origin	Age years	Sex	TB form	Test results at time of delamanid request	Resistance profile	Expert panel consulted and indication for delamanid	Drugs used prior to delamanid	Started delamanid	Treatment outcome or interim treatment response
1	Italy	13	M	P and EP	SS+/C+ (MGIT), Xpert+	XDR-TB: H, R, Z, E, S, Rfb, Amk, Cm, Km, Lfx, Mfx, Ofx, Eto, Pto, HdH	TB Consilium: extensive resistance to SLDs, drug toxicity and limited options for treatment	H, Z, E, Amk, Mfx, Eto, PAS, Tzd, Amx/Clv, Clr, Cfz, Lzd, Mpm	Yes	Cured
2	South Africa	17	F	P	SS+/C+, Xpert+	XDR-TB: H, R, Amk, Km, Ofx, Eto	TB Consilium: extensive resistance to SLDs and severe clinical presentation	H, Z, E, Cm, Km, Mfx, Eto, PAS, Tzd, Cfz, HdH	No [#]	
3	South Africa	13	M	P	SS+/C+, Xpert+	XDR-TB: H, R, Amk, Ofx	TB Consilium: extensive resistance to SLDs and severe clinical presentation	Z, E, Cm, Km, Mfx, Eto, PAS, Tzd, Amx/Clv, Clr, Cfz, Lzd	Yes	Currently culture negative, good clinical response, delamanid completed
4	South Africa	13	F	P	SS-/C+ (MGIT), Xpert+	XDR-TB: H, R, Amk, Ofx	TB Consilium: extensive resistance to SLDs and severe clinical presentation	E, Z, Cm, Mfx, Eto, PAS, Tzd, Cfz, HdH, Lzd	Yes	Currently culture negative, good clinical response, delamanid ongoing
5	South Africa	8	M	P	SS+/C+ (MGIT), Xpert MTB+, R resistant	Pre-XDR: H, R, Amk, Cm, Km, Eto	TB Consilium: extensive resistance to SLDs and severe clinical presentation	Z, Amk, Mfx, Eto, Tzd	Yes	First culture not yet available
6	Namibia	9	M	P and EP	SS-/C-, lymph C+ (MGIT)	XDR-TB: H, R, E, S, Amk, Cm, Km, Lfx, Mfx, Ofx, Eto, PAS, Cs, HdH	TB Consilium: extensive resistance to SLDs and severe clinical presentation	Z, Cm, Mfx, PAS, Cs, Amx/Clv, Clr, Cfz, HdH	No [¶]	
7	South Africa	12	F	P	SS-/C+ (MGIT), Xpert indeterminate	XDR-TB: H, R, S, Amk, Cm, Km, Ofx, Eto, Pto, HdH	TB Consilium: extensive resistance to SLDs and severe clinical presentation	H, R, Z, E, Eto, Tzd, Lfx	Yes	Currently culture negative, good clinical response, delamanid ongoing
8	India	12	F	P	SS+/C+ (MGIT)	XDR-TB: R, H, Z, E, S, Amk, Cm, Km, Mfx, Ofx, Eto, PAS, Cs, Lzd	TB Consilium: extensive resistance to SLDs and severe clinical presentation	E, Z, Cm, Mfx, PAS, Cs, Amx/Clv, Clr, Cfz, Lzd, Mpm	Yes	First culture not yet available
9	India	17	F	P	SS+/C+ (MGIT)	XDR-TB: H, R, E, S, Amk, Cm, Km, Mfx, Ofx, Eto, PAS	endTB committee: extensive resistance to SLDs	H, R, Z, E, S, Km, Mfx, Pto, PAS, Cs, Amx/Clv, Clr, Cfz, Lzd	Yes	Currently culture negative, good clinical response, delamanid completed
10	India	15	F	P	SS+/C+ (MGIT)	XDR-TB: H, R, E, S, Amk, Km, Ofx, Eto, PAS, Cfz	endTB committee: extensive resistance to SLDs	H, R, Z, E, Km, Mfx, Eto, PAS, Cfz, Lzd	Yes	Currently culture negative, good clinical response, delamanid completed
11	India	16	M	P	SS-/C+ (MGIT)	XDR-TB: H, R, E, S, Amk, Cm, Km, Mfx, Ofx, Eto, PAS	endTB committee: failure of previous treatment and extensive resistance to SLDs	H, R, Z, E, Rfb, Cm, Km, Lfx, Mfx, Eto, PAS, Cs, Amx/Clv, Cfz, HdH, Lzd	Yes	Culture negative, good clinical response, delamanid completed
12	India	13	F	P and EP (lymph node)	SS+/C+ (MGIT), Xpert MTB+, R resistant	XDR-TB: H, R, E, Z, S, Amk, Cm, Km, Mfx, Ofx, Eto, PAS, Cs	endTB committee: extensive resistance to SLDs	H, R, Z, E	No ⁺	
13	Georgia	16	M	P	SS+/C+ (MGIT), Xpert MTB+, R resistant	MDR-TB: H, R, E, Z	endTB committee: no improvement with SLDs (still smear positive after 3 months of treatment)	E, Z, Cm, Mfx, Cs, PAS, Lzd	Yes	Currently culture negative, good clinical response, delamanid ongoing


Continued

TABLE 1 Continued

Patient	Country of origin	Age years	Sex	TB form	Test results at time of delamanid request	Resistance profile	Expert panel consulted and indication for delamanid	Drugs used prior to delamanid	Started delamanid	Treatment outcome or interim treatment response
14	Georgia	17	M	P	SS-/C+ (MGIT), Xpert MTB+, R resistant	Pre-XDR (FQ): H, R, E, S, Ofx	endTB committee: no improvement with SLDs (culture positive after 7 months of treatment, progression of infiltrates and cavities)	H, Z, E, Cm, Lfx, Mfx, Pto, PAS, Cs	Yes	Culture negative, good clinical response, delamanid ongoing
15	Georgia	15	M	P	SS-/C+ (MGIT), HAIN MTB+, R resistant	XDR-TB: H, R, E, S, Km, Ofx	endTB committee: extensive resistance to SLDs and severe clinical presentation (bilateral lesions)	H, R, Z, E, Cm, Lfx, Mfx, Pto, PAS, Cs, Cfz, Lzd	Yes	Culture negative, good clinical response, delamanid completed
16	Georgia	17	M	P	SS+/C+ (MGIT), Xpert MTB+, R resistant	Pre-XDR (FQ): H, R, E, S, Ofx	endTB committee: no clinical or radiological improvement with SLDs	E, Z, Cm, Lfx, Mfx, Pto, PAS, Cs, Amx/Clv, Clr, Cfz	Yes	Culture negative, good clinical response, delamanid completed
17	Russia	16	F	P	SS+/C+ (MGIT), Xpert MTB+, R resistant	XDR-TB: H, R, S, Cm, Lfx	endTB committee: extensive resistance to SLDs and severe clinical presentation (bilateral lesions)	Z, Cm, Lfx, Pto, PAS, Cs	Yes	Currently culture negative, good clinical response, delamanid ongoing
18	Armenia	16	M	P	SS+/C+ (MGIT), Xpert MTB+, R resistant	Pre-XDR (FQ): H, R, Z, E, Amk, Cm, Pto	endTB committee: extensive resistance to SLDs and drug toxicity	Cm, Lfx, Pto, PAS, Cs, Amx/Clv, Cfz	Yes	Currently culture negative, good clinical response, delamanid ongoing
19	Swaziland	15	M	P	SS+/C+ (MGIT), Xpert MTB+, R resistant	XDR-TB: H, R, E, S, Cm, Km, Mfx	endTB committee: failure of previous treatment and extensive resistance to SLDs	Z, Km, Lfx, Pto, PAS, Cs	Yes	First culture not yet available

TB: tuberculosis; SS: sputum smear; C: culture; M: male; F: female; P: pulmonary; EP: extrapulmonary; MGIT: Mycobacteria Growth Indicator Tube (Becton, Dickinson and Company, Franklin Lakes, NJ, USA); Xpert: Xpert *Mycobacterium tuberculosis* (MTB)/rifampicin test (Cepheid, Sunnyvale, CA, USA); XDR: extensively drug-resistant; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; S: streptomycin; Rfb: rifabutin; Amk: amikacin; Cm: capreomycin; Km: kanamycin; Lfx: levofloxacin; Mfx: moxifloxacin; Ofx: ofloxacin; Eto: ethionamide; Pto: prothionamide; HdH: high-dose isoniazid; SLDs: second-line drugs; PAS: para-aminosalicylic acid; Tzd: terizidone; Amx/Clv: amoxicillin plus clavulanate; Clr: clarithromycin; Cfz: cefazolin; Lzd: linezolid; Mpm: meropenem; Cs: cycloserine; MDR: multidrug-resistant; FQ: fluoroquinolones; HAIN: GenoType MTBDRplus (Hain Lifescience GmbH, Nehren, Germany). #: after inclusion in delamanid compassionate use programme, treating clinicians decided to withdraw the request for delamanid for this patient due to adverse effects and poor treatment adherence; †: awaiting import permit from the relevant authorities; *: patient withdrawn from compassionate use programme for programmatic reasons.



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