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CASE REPORT

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Bedaquiline in the Treatment of Multidrug-Resistant Tuberculosis in Pediatric Patients

Bedaquilina en el tratamiento de tuberculosis multirresistente en pediatría

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) arises from strains of *Mycobacterium tuberculosis* with *in vitro* resistance to at least isoniazid and rifampicin, two key first-line drugs for treatment. Annually, around 30,000 children worldwide contract this form of tuberculosis, and less than 5 % receive adequate treatment. The approach for these cases should follow the sensitivity profile of the germ, trying to achieve the patient's cure with the fewest possible complications and sequelae, and to prevent community transmission of the disease. In 2022, the World Health Organization (WHO) recommended bedaquiline for the treatment of MDR-TB in adults and children of all ages. Our objective is to communicate our experience in the administration of bedaquiline in children and adolescents in the context of MDR-TB treatment according to the latest recommendations.

Key words: Pulmonary tuberculosis; MDR-TB; Treatment; Bedaquiline; Children

RESUMEN

La tuberculosis multirresistente (TB-MDR) surge de cepas de *Mycobacterium tuberculosis* con resistencia *in vitro* al menos a isoniacida y rifampicina, dos drogas de primera línea claves para el tratamiento. Anualmente, alrededor de 30 000 niños en el mundo contraen esta forma de tuberculosis, y menos del 5 % recibe tratamiento adecuado. El enfoque para estos casos debe seguir el perfil de sensibilidad del germen, tratando de lograr la curación del paciente con el menor número de complicaciones y secuelas posibles, y prevenir la transmisión comunitaria de la enfermedad. En 2022 la Organización Mundial de la Salud recomendó la bedaquilina para el tratamiento de la TB-MDR en adultos y niños de todas las edades. Nuestro objetivo es comunicar nuestra experiencia sobre la administración de bedaquilina en niños y adolescentes en el contexto del tratamiento de la TB-MDR de acuerdo con las últimas recomendaciones.

Palabras clave: Tuberculosis pulmonar; TB-MDR; Tratamiento; Bedaquilina; Niños

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INTRODUCTION

Tuberculosis (TB) that shows drug resistance is uncommon in the pediatric population of Argentina. Out of the 10,603 cases of individuals under 20 years old reported to the National TB Control Program in the last 5 years, 194 cases have been identified with some form of resistance to antituberculous medications.[1] The treatment of these cases requires a specific therapeutic intervention, with greater precision and efficacy than for TB caused by strains of *Mycobacterium tuberculosis* (Mtb) that are sensitive to first-line drugs.

Multidrug-resistant tuberculosis (MDR-TB) is a disease caused by mycobacteria that show *in vitro* resistance to isoniazid (H) and rifampicin (R), two of the main first-line drugs in treatment. Cases with resistance to rifampicin (RR-TB) are associated with poorer therapeutic responses, so it is suggested that these patients be treated with the same regimens as MDR-TB plus isoniazid.[2]

The situation becomes even more complicated when the resistance is broader and includes second-line drugs, as the case of pre-extensively drug-resistant TB (pre-XDR). This variant involves MDR and at least one of the two fluoroquinolones, levofloxacin (Lfx) or moxifloxacin (Mfx), which are fundamental in the treatment of MDR-TB. Extensively drug-resistant TB (XDR-TB) adds resistance to bedaquiline (Bdq) and/or linezolid (Lzd), thus increasing the complexity of the treatment.[2]

In these cases, the regimen to be used should be in accordance with the Mtb's sensitivity pattern, aiming to achieve patient cure with the fewest possible complications, adverse effects, and sequelae, and to prevent the transmission of the disease in the community.

In 2022, the WHO recommended the use of Bdq for the treatment of MDR/RR-TB in adults and children of all ages.[3] Bdq has played an increasingly relevant role in the treatment of drug-resistant TB, avoiding the use of injectable medications and progressing towards fully oral treatment regimens. Our objective is to communicate our experience in the administration of Bdq in children and adolescents in the context of MDR/RR-TB treatment according to the latest recommendations of the WHO.

Case 1: A 16-year-old female patient diagnosed with MDR-TB. The patient had severe cavitary involvement in both lungs and right pneumothorax (Figure 1 A). She was referred to our hospital due to poor progression and adverse effects from several of the drugs she had been administered (severe hearing loss from amikacin, hepatotoxicity from ethionamide (Eto), and seizures from cycloserine (Cs)). Treatment was indicated with Bdq, Mfx, Lzd, para-aminosalicylic acid (PAS), amoxicillin-clavulanate plus meropenem, and clofazimine (Cfz), according to the initial sensitivity tests. The dosage of Bdq used was 400 mg daily for 14 days, followed by 200 mg three times a week.

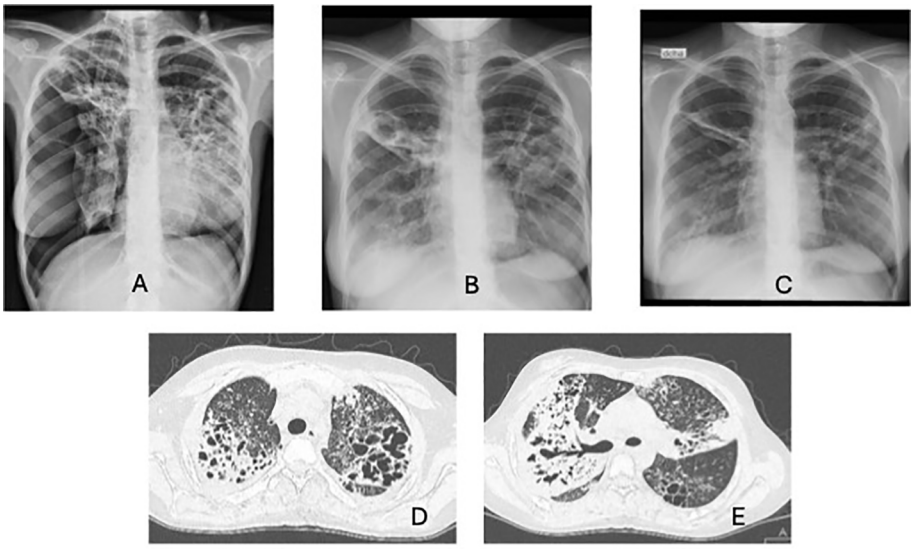

Figure 1. A, B and C: Chest X-rays of case 1 at the start and after 8 months and 12 months of treatment. D and E: Chest CT scans of case 2 showing thick-wall cavities and multiple cystic and varicose bronchiectasis in the upper lobes of both lungs.

On the 10th day, the electrocardiogram showed a prolonged QTc interval, elevated liver enzymes, and lymphopenia; Mfx was discontinued and the dose of Lzd was reduced. With the normalization of the Qtc and liver enzymes, and the resolution of lymphopenia, she continued the antituberculous treatment with good clinical and radiological evolution (Figure 1 B). After 6 months of treatment, Bdq was discontinued and Mfx was administered again, with no new abnormalities observed neither in the electrocardiogram nor in the laboratory tests. Despite the fact that a clear improvement was observed after 12 months of treatment (Figure 1 C), this was compromised by the restrictions imposed due to COVID-19. The patient continued receiving treatment at home, but unfortunately she experienced a deterioration in the following months, resulting in the patient's death.

Case 2: A 16-year-old female patient diagnosed with MDR-TB under treatment with Cs, Eto, ethambutol (E), and Mfx based on sensitivity tests. She was referred to our center due to hepatotoxicity and worsening radiological findings. She showed bilateral pulmonary involvement with cavitation (Figures 1 D and E). The treatment regimen was changed to Cs, Lfx, and Lzd; on the 13th day, after normalization of liver enzymes, Bdq and Cfz were added. She did not present any electrocardiographic abnormalities, with the highest QTc value being 0.44 seconds on day 38, which subsequently decreased during the rest of the treatment. The dosage of Bdq used was 400 mg daily for 14 days, followed by 200 mg three times a week. After 6 months, Bdq was discontinued, and treatment continued with Cfz, Lzd, Lfx, and Cs. At present, she is still undergoing treatment with good clinical and radiological evolution.

Case 3: A 2-year and 9-month-old previously healthy female patient presented with a 30-day history of cough and intermittent fever. The nasopharyngeal swab for COVID-19 tested positive. She was being evaluated due to contact with her mother, who had MDR-TB. She tested positive on the PPD (Purified Protein Derivative) test. She had multifocal pulmonary involvement without cavitation (Figure 2 A). Gastric lavage showed Mtb complex detected by Xpert with indeterminate rifampicin resistance, and culture was positive for pre-XDR TB based on drug sensitivity tests. Treatment was initiated with Bdq, Cfz, Lzd, Cs, and E. She received Bdq for 6 months without presenting QTc abnormalities (0.38 seconds) in cardiological or laboratory controls. Currently, she shows improvement both clinically and radiologically, without experiencing any adverse effects.

Case 4: A 1-year and 4-month-old female patient was referred to the hospital due to contact with her mother and sister, who had pre-XDR TB (case 3). Upon admission, she presented with a 1-month history of cough, and the nasopharyngeal swab tested positive for COVID-19. She tested positive on the PPD test. She showed unifocal pulmonary involvement without cavitation (Figure 2 B). The gastric lavage culture was positive for pre-XDR TB with the same resistance pattern as her sister. She received treatment with Bdq, Cfz, Lzd, Cs, and E. Cardiological controls showed no QTc abnormalities (maximum value 0.40 seconds,

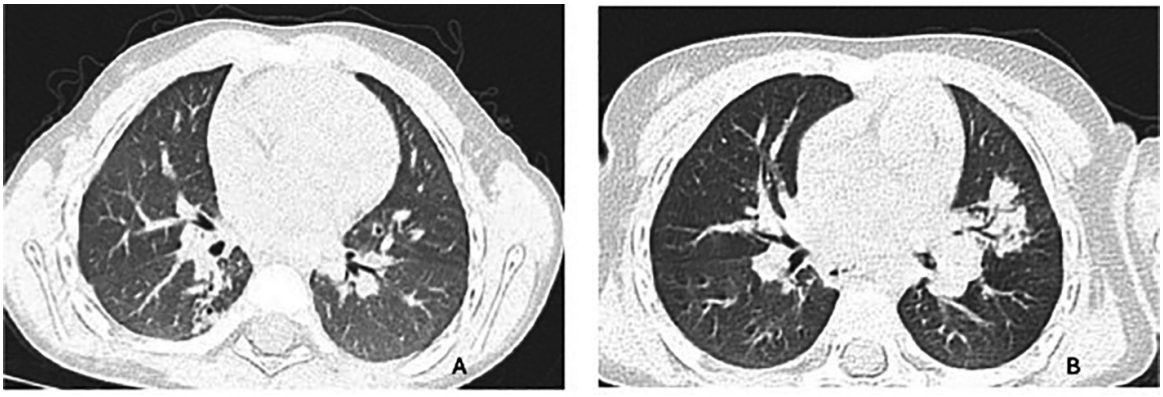

Figure 2. Image A: Chest CT scan for case 3 shows multiple calcified nodular images in the posterior segment of the right lower lobe. There is also a patchy dense area with bronchiectasis. Image B: Chest CT scan for case 4 shows left hilar lymph node enlargement and patchy consolidation of the lung parenchyma with air bronchogram in the lingula.

at the second month of treatment), and there were no hematological or hepatic alterations. Bdq was discontinued after 6 months, and she continues to respond well to treatment, with good tolerance.

The Bdq dosage used in cases 3 and 4 was calculated based on the weight of the girls during clinical controls, according to international recommendations.[2,5,7]

DISCUSSION

Each year, approximately 30,000 children worldwide are affected by these variants of TB, and less than 5 % receive adequate treatment.[2,4] In Argentina, of the 12,569 TB cases reported to the National Tuberculosis Control Program in 2021, 270 were microbiologically confirmed as pulmonary TB patients with some form of antituberculous drug resistance. 154 of these (57 %) showed resistance to rifampicin (R), of which 110 (71.5 %) were cases of MDR-TB and 3 were pre-XDR TB. Additionally, 4 RR-TB cases were identified among extrapulmonary cases, and 7 had no recorded location.[6] In total, 21 MDR/RR-TB cases affected patients under 20 years old.[1] The possibility of transmitting these mycobacterial strains among children and adolescents is a public health issue that requires special attention.[2]

The four patients we are reporting received individualized treatments with Bdq, which included at least four drugs effective against the microorganism. In the pediatric MDR/RR-TB population of all ages, the use of Bdq as part of personalized treatment regimens is recommended.[2,3,7,8] However, pharmacokinetic and safety data are limited, especially for patients under 5 years old.[7]

The recommended duration of Bdq treatment is six months, continuing treatment with other medications. In some cases, such as those showing resistance to fluoroquinolones or intolerance to Lzd, extending the use of Bdq beyond six months can be considered, always under the supervision of a pediatric MDR-TB expert and with rigorous follow-up from the start of treatment.[7,8]

In general, children with less severe MDR/RR-TB should be treated for less than 18 months. However, in cases of extensive disease, the treatment duration may need to be prolonged, depending on factors such as clinical evolution, TB location (osteoarticular or meningeal), resistance profile, and the number of effective drugs available.[7]

Proper dosing of the drugs used in the treatment of MDR/RR-TB in children is crucial to minimize adverse effects, ensure effective outcomes, and prevent the appearance of additional resistance.[2] In the case of Bdq, it starts with a daily loading dose for the first two weeks, followed by a maintenance dose administered three times a week (e.g., Monday, Wednesday, and Friday). For children under 3 months old, a daily dose of 30 mg of Bdq is recommended for 14 days, followed by 10 mg three times a week, regardless of weight. In children aged 3 to 6 months, the initial dose is 60 mg of Bdq daily for 14 days, followed by 20 mg three times a week, also regardless of weight. For children aged 6 months or older, the dosage should be adjusted according to their body weight[2] (Table 1).

It is especially important to perform monthly weight monitoring in children and adolescents during the course of treatment. Improved nutrition is expected during this period, so doses should be adjusted as children gain weight.

TABLE 1. Dose of Bdq in children aged 6 months or older. Prepared according to the International Guidelines cited in References 2, 7 and 8

Bedaquiline Dosage based on body weight for children 6 months or older	
Weight range (kg)	**Dose**
3-6.99 Kg	60 mg daily for 14 days, followed by 20 mg three times a week
7-9.99 Kg	80 mg daily for 14 days, followed by 40 mg three times a week
10-15.99 Kg	120 mg daily for 14 days, followed by 60 mg three times a week
16-29.99 Kg	200 mg daily for 14 days, followed by 100 mg three times a week
> 30 Kg	400 mg daily for 14 days, followed by 200 mg three times a week

The absorption of Bdq significantly improves when administered with food, especially high-fat foods. Therefore, whenever possible, it is recommended to administer it with food. Dispersible formulations with a pleasant taste have been developed for the pediatric population, such as the 20 mg of Bdq.[7]

In the case of Bdq, it has been demonstrated that tablets for adults maintain their effectiveness when they are crushed and mixed with water, compared to tablets taken whole. This crushed form, divided according to the child's weight, can be used to treat RR/MDR-TB, especially when dispersible tablets are not available or to facilitate administration in children who have difficulty swallowing whole tablets.[7,8]

Additionally, 100 mg adult tablets can be used to prepare Bdq syrup formulations, both with and without sugar, which can be stored at room temperature for 15 or 30 days, respectively.[9]

Potential adverse effects associated with Bdq include headache, nausea, liver dysfunction, QTc interval prolongation, and arthralgia. It is advisable for patients receiving a combination of drugs that may prolong the QTc interval, such as clofazimine, bedaquiline, delamanid, or fluoroquinolones, to undergo regular monitoring with electrocardiograms.[7,10]

Conclusion: Since the recommendation to use Bdq in pediatrics is relatively recent, there are few case reports available, especially in children under 6 years of age. The cases we report represent the first experiences of using Bdq in children and adolescents in our country. Our patients showed good tolerance to this medication.

Conflict of interest
None to declare.

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