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Practical Pharmacological Aspects of Drugs Used for the Treatment of Drug-Resistant Tuberculosis in Adults and Children

Aspectos farmacológicos prácticos de las drogas para el tratamiento de la tuberculosis drogorresistente en adultos y pediatría

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ABSTRACT

The emergence of resistant strains of *Mycobacterium tuberculosis* to multiple drugs and the difficulties of their diagnosis and treatment constitute a challenge to global public health. To face this challenge, new anti-tuberculosis drugs, such as bedaquiline, pretomanid, and delamanid, as well as replacement drugs, such as fluoroquinolones, linezolid and clofazimine, are used. Based on the evidence provided by multicenter studies, drugs associated with a better prognosis of drug-resistant tuberculosis have been discovered and, recently, a new classification has been proposed, as well as new totally oral regimens. In this review, we describe current treatment regimens and practical pharmacological aspects required when prescribing new drug-resistant tuberculosis treatment regimens.

Key words: Tuberculosis; Drug-resistance; MDR-TB; Pharmacology

RESUMEN

La emergencia de cepas resistentes de *Mycobacterium tuberculosis* a múltiples drogas, las dificultades de su diagnóstico y tratamiento constituyen un desafío a la salud pública mundial. Para afrontar esta situación, se emplean nuevas drogas antituberculosis, como bedaquilina, pretomanid y delamanid, así como drogas repropuestas, como fluoroquinolonas, linezolid y clofazimina. Con base en la evidencia brindada por estudios multicéntricos, se han descubierto fármacos asociados a un mejor pronóstico de la tuberculosis drogorresistente y, recientemente, se ha propuesto una nueva clasificación, así como nuevos esquemas totalmente orales. En esta revisión, describimos los esquemas de tratamiento actuales y los aspectos farmacológicos prácticos necesarios a la hora de la prescripción de los nuevos regímenes de tratamiento de la tuberculosis drogorresistente.

Palabras clave: Tuberculosis; Drogorresistencia; TB-MDR; Farmacología

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INTRODUCTION

The global threat of drug-resistant tuberculosis (DR-TB) has promoted the research of new treatment regimens, new drugs, and repurposed drugs[1] (not originally sold for TB, such as fluoroquinolones, linezolid and clofazimine) together with the traditionally called "second-line drugs" for the purpose of improving the efficacy of treatment of these forms of the disease.

The objective of this review is to briefly analyze current treatment regimens according to international rules, and to describe dosages in adults and children, mechanisms of action, adverse reactions, and use in cases of renal and liver failure, pregnancy and tuberculous meningitis, of available drugs to treat drug-resistant TB. Thorough review on DR-TB found in[2].

There are different DR-TB categories[3-5]: monoresistant TB, caused by strains of *Mycobacterium tuberculosis* (*Mtb*) and resistant to only one drug, the most concerning being monoresistance to isoniazid (Hr) and rifampicin (Rr); multidrug-resistant TB (MDR-TB), which shows resistance to at least isoniazid (H) and rifampicin (R); pre-extensively drug resistant TB (pre-XDR-TB), which is MDR and also shows resistance to one of the antituberculous fluoroquinolones (levofloxacin or moxifloxacin); and at last, extensively resistant (XDR-TB), which apart from being pre-XDR-TB, is also resistant to at least bedaquiline or linezolid (group A of the World Health Organization, WHO).

In 2018, the WHO published a new classification of drugs to be used for DR-TB, updated in 2020[6] (**Table 1**) and based on the meta-analysis of individual MDR-TB patients data published by Ahmad et al[7].

Treatment regimens of Hr-TB, Rr-TB and MDR-TB

The treatment recommended by the international guidelines for Hr-TB is a 6-month regimen with four drugs, without initial phase: levofloxacin, pyrazinamide, rifampicin and ethambutol. Treatment duration is determined by the need to complete 6 months of levofloxacin[6, 8].

Rr-TB is a category that arose from the advent of the rapid molecular method for diagnosis called Xpert Mtb RIF, which detects in *Mtb,* with almost 100% specificity, the presence of the five most common mutations of the *RpoB* gene that explain resistance to R[9]. Given the fact that approximately 80% of the Rr strains show additional resistance to H[10] and that a first-line drug for the treatment of TB has been lost, Rr-TB should be treated as MDR-TB[6, 8].

According to new recommendations, MDR-TB can be treated with a 100% oral regimen including the three drugs of the WHO Group A (bedaquiline, linezolid, fluoroquinolone), together with one or two drugs from Group B (cycloserine or clofazimine). Bedaquiline is administered the first 6 months (***see* Table 2**), and the other three or four drugs are given throughout the whole treatment, which lasts 18 months (it may be shortened in mild cases). Group C drugs would be left as replacement of Groups A and B if they can't be used due to resistance or adverse reactions[6, 8].

Alternatives to isoniazid and rifampicin for the treatment of DR-TB

Tables 2 and 3 show every drug, mechanisms of action, dosage in adults and children, most common adverse reactions, use in renal and liver failure and pregnancy and passage into CSF (ce-

TABLE 1. WHO classification of drugs for the treatment of MDR-TB and their inclusion in a treatment regimen[6]

Group	Drug
A (include the three drugs, unless they can't be indicated due to toxicity or resistance)	levofloxacin or moxifloxacin bedaquiline linezolid
B (include one or both drugs, unless they can't be indicated due to toxicity or resistance)	clofazimine cycloserine or terizidone*
C (add to complete the regimen if one or more drugs from group A and B can't be administered)	ethambutol delamanid* pirazinamide carbapenems/clavulanate amikacin (or streptomycin) ethionamide or prothionamide p-aminosalicylic acid

*Not yet available in Argentina

TABLE 2. Drugs from WHO Groups A and B used in the treatment of drug-resistant TB[6, 8, 15-22]

Drug (presentation)	Mechanism of action	Dose for adults	Paediatric dose (<15 years)	Renal failure	Liver failure	Severe adverse reactions (%)	Pregnancy	Passage into CSF
Bedaquiline (100 and 20 mg* tablets) Administer with food	Inhibits mycobacterial ATP (adenosine triphosphate)-synthase.	400 mg/d for 2 weeks; then 200 mg, three times a week.	<16 kg of weight: 6 mg/kg/d for 2 weeks, then 3-4 mg/kg/d. 16-30 kg: 200 mg/d for 2 weeks, then 100 mg, three times a week. >30 kg: the same as adults.	UD	UD in mild to moderate LF. Severe LF: do not administer	2.5% Prolonged QTc (corrected QT) interval, nausea and vomiting, potential hepatotoxicity, arthralgia and myalgia. Close ECG (electrocardiogram) monitoring, especially if combined with other drugs associated with QTc prolongation. Do not use if previous QTc is >450 ms. Discontinue if QTc > 500 ms. Interaction with ARVs. Persists in the organism for up to 6 months after finishing its administration, with therapeutic levels and possibility of ARs.	Non-teratogenic in animals. Insufficient evidence in humans.	IE, presumably scarce passage into CSF.
Levofloxacin (250, 500 and 750 mg tablets; 500 mg vial; 100 mg tablets)	Inhibits mycobacterial DNA gyrase.	PO = EV, 750-1000 mg/d	PO = EV, 15-20 mg/kg/d. Up to 1000 mg/d.	Adjust according to clearance or US post-dialysis.	Rarely hepatotoxic. Can be administered.	4.1% Low toxicity and good tolerance. Arthralgia, myalgia, tendinitis, photosensitivity, QT prolongation (rare) ** Psychosis, convulsions, peripheral neuropathy.	Only if the benefit is greater than the risk (Class C).	70-80%
Moxifloxacin (400 and 100 mg* tablets	Inhibits mycobacterial DNA gyrase	400 mg/d High dose: 800 mg/d <55 kg: 15 mg/k/d	10-15 mg/kg, once a day. Unspecified high doses.	UD (hepatic metabolism)	Potentially hepatotoxic. Levofloxacin is preferred	2.9% Toxicity profile similar to levofloxacin, though it prolongs the QTc more frequently. Monitor QTc, especially when combining it with other drugs with the same ARs **	Class C	70-80%
Linezolid (600 mg tablets, 600 mg injectable solution for endovenous administration)	Inhibits protein synthesis.	PO = EV, 600 mg/d Some studies reduce dosage to 300 mg/d due to ARs.	PO = EV, <15 kg: 15 mg/kg/d; ≥15 kg: 10-12 mg/kg/d. Up to 600 mg/d.	UD	UD	17.2% Myelosuppression, anemia, leukopenia, thrombocytopenia, peripheral neuropathy, optic neuritis, lactic acidosis. Pyridoxine (100-200 mg/d) could reduce adverse effects; in paediatric patients: 1-2 mg/kg/d.	Class C	30-70%
Clofazimine (50 and 100 mg gelcaps)	Alterations in cell membrane.	100 mg/d	2 to 5 mg/kg/d. Up to 100 mg/d.	UD	Potentially hepatotoxic.	3.6% Skin pigmentation, ichthyosis, xerosis, abdominal colics, corneal deposits; prolongs the QTc.**	Do not administer.	IE
Cycloserine and terizidone (250 mg capsules and 125 mg* microcapsules	Inhibit the synthesis of the mycobacterial wall.	250 mg every/ 8 h (total dose: 15 mg/kg/d)	15-20 mg/kg/d in three divided doses. Up to 750 mg/d	Adjust according to clearance.	UD	7.8% Neurotoxicity (convulsions, psychosis, suicide attempt). Polyneuritis. Pyridoxine (100-200 mg/d) could reduce neurotoxicity; in paediatric patients: 1-2 mg/kg/d.	Class C	80%-90%

ARV: antiretrovirals; Class C: only if the benefit of its administration is greater than the risk; UD: usual dose; EV: endovenous; V: vial; IE: insufficient evidence; LF: liver failure; AR: adverse reactions; PO: oral route

* Paediatric formulations not yet available in Argentina.

**ECG with QTc determination when used in combination with other drugs that also prolong the QTc

TABLE 3. Drugs from WHO Group C used in the treatment of drug-resistant TB[6, 8, 15-24]

Drug (presentation)	Mechanism of action	Dose for adults	Paediatric dose (<15 years)	Renal failure	Liver failure	Severe adverse reactions (%)	Pregnancy	Passage into CSF
Amikacin (500 mg amp.)	Inhibits mycobacterial protein synthesis.	IM = EV, 1000 mg/d (15 mg/kg/d), three times a week, after conversion of culture	IM = EV, 15-20 mg/k/d. Up to 1000 mg/d	Avoid use in RF. UD post-dialysis	UD	10.3% Ototoxicity Nephrotoxicity Peripheral neuropathy	Congenital deafness. Contraindicated	10%-20% Increases with meningeal inflammation.
Delamanid (50 mg tablets) Not available in Argentina yet	Alters the synthesis of mycobacterial cell wall and respiration.	≥ 50 kg: 100 mgc/12 h. 30-50 kg: 50 mgc/12 h. Administer with food.	20 kg to 34 kg: 50 mg in 2 divided doses. ≥ 34 kg: same dose as adults. Administer with food.	UD in moderate RF. Not recommended in severe RF.	UD in mild to moderate LF. Severe LF: do not administer.	% AR: not specified (low toxicity). Prolonged QTc interval**, nausea and vomiting. Weak interaction with antiretrovirals. Strong protein binding. Do not use with albuminemia (< 2.8 g/dL).	Teratogenic in animals.	IE
Ertapenem	Inhibits the synthesis of the mycobacterial wall.	IM, 1000 mg/d	Limited data on paedriatic tuberculosis.	Idem imipenem-cilastatin.	Idem imipenem-cilastatin	Idem imipenem-cilastatin.	Class C	IE
Streptomycin (1000 mg vial)	Inhibits mycobacterial protein synthesis.	IM = EV, 1000 mg/d (15 mg/kg/d), three times a week, after conversion of culture.	IM = EV, 15-20 mg/k/d. Up to 1000 mg/d.	Avoid use in RF. UD post-dialysis.	UD	4.5% Ototoxicity Nephrotoxicity Skin allergy	Congenital deafness. Contraindicated.	10%-20% Increases with meningeal inflammation.
Ethambutol (400 mg tablets, 100 mg disp. Tablets	Inhibits the synthesis of the bacterial wall.	25 mg/kg/d	15-25 mg/kg/d	Adjust according to clearance.	UD	4% Optic neuritis, peripheral neuropathy, nausea and vomiting. Monitor visual acuity and color vision.	Can be administered	20%-30%
Ethionamide/ prothionamide (250 mg tablets, 125 mg disp. tablets	Inhibits synthesis of mycolic acid.	250 mg e/8 h (15 mg/kg/d)	15-20 mg/kg/d. Up to 1000 mg/d	UD	Not recommended	9.5% Polyneuritis, nausea, vomiting, diarrhea, hepatitis, hypothyroidism, metallic taste, gynecomastia.	Teratogenic in animals. Contraindicated.	80%-90%
Imipenem-cilastatin (1000 mg vial in fixed combination with cilastatin)	Inhibits the synthesis of the mycobacterial wall	EV: 500 mg every/6 h together with 125 mg of clavulanate every/8 h PO ***	Not indicated in children under 15 years (meropenem is used).	Adjust according to clearance or US post-dialysis.	Not recommended due to clavulanate.	Rare ARs. Hypernatremia, convulsions (rare), hepatotoxicity (clavulanate), skin allergy.	Class C	Good passage into CSF, 50% of pulmonary concentration.
Meropenem (1000 mg vial)	Inhibits the synthesis of the mycobacterial wall	EV, 1000 mg every/8 h, together with 125 mg of clavulanate every/8 h	EV, 20-40 mg/kg/d every 8 h (with clavulanate, 15 mg/k/d). Up to 3000 mg/d.	Idem imipenem-cilastatin.	Idem imipenem-cilastatin.	Idem imipenem-cilastatin.	Class C	Similar to imipenem.
PAS (para-aminosalicylic acid) (4 g sachet, granules)	Inhibits synthesis of folic acid.	8-12 g/d, divided in 2-3 doses.	200-300 mg/kg/d, divided in 1 to 3 doses according to tolerance. Up to 12 g/d.	UD	Potentially hepatotoxic.	14.3% Nausea, vomiting, diarrhea, hepatitis, hypothyroidism (worsens with the Eto-PAS combination	Class C	IE
Pirazinamide (250, 400 and 500 mg tablets, 150 mg disp. tablets*)	Prodrug, the pyrazinoic acid inhibits the synthesis of the mycobacterial membrane.	PO, 25 mg/kg/d.	PO, 30-40 mg/kg/d. Up to 2000 mg/d.	Adjust according to clearance or US post-dialysis.	Contraindicated	8.8% Food intolerance, toxic hepatitis, hyperuricemia, skin allergy, polyneuritis.	Can be administered.	90%-100%
Pretomanid (200 mg tablets) Approved only for BPal regimen	Alters the synthesis of cell wall and respiration.	PO, 200 mg/d.	The BPaL regimen is not indicated in children at present.	Moderate RF: UD. Severe RF: do not administer.	Not recommended in moderate or severe liver failure.	% ARs: not specified. Prolonged QT interval, nausea and vomiting. Infertility in animals. Do not administer in combination with efavirenz or PI (protease inhibitor).	Insuficient data	Not specified

ARV: antiretrovirals; BPaL: bedaquiline-pretomanid-linezolid; Class C: only if the benefit of its administration is greater than the risk; disp. tablets: dispersible tablets; UD: usual dose; EV: endovenous; V: vial; IE: insufficient evidence; LF: liver failure; IM: intramuscular; RF: renal failure; BW: body weight; AR: adverse reactions; PO: oral route.
* Paediatric formulations not yet available in Argentina.
**ECG with QTc determination when used in combination with other drugs that also prolong the QTc.
*** As amoxicillin-clavulanate, 500 mg/125 mg. Clavulanate is an inhibitor of the beta-lactamase of *Mycobacterium tuberculosis*.
# Recommended by the WHO for children of all ages.

rebrospinal fluid), a fundamental element in the treatment of tuberculous meningitis.

Treatment of XDR-TB[11-13]

As seen in its definition, it implies resistance to at least H, R, one fluoroquinolone (levo or moxifloxacin) and bedaquiline or linezolid. From that minimum base of the definition (which already creates a complicated situation but still leaves other therapeutic options), resistance can be extended practically to all anti-TB drugs. Also, the antibiogram of multi-treated patients doesn't correlate very well with the clinical picture, as in MDR-TB, and it is more common to find differences between the phenotypic and genotypic methods. So, it is important to ask the patients detailed questions regarding their previous treatments and clinical and bacteriological responses. To sum up, the design of a regimen for XDR-TB is individualized, and no guidelines can be provided as in other forms of DR-TB. Regimens are indicated with drugs that show persistent antibiogram sensitivity plus those that weren't previously used, trying to get a minimum number of potentially effective drugs (3 or 4). In an effort to improve the diagnosis of these patients, the bedaquiline-delamanid combination has been used, as well as bedaquiline alone, for one year of treatment. New regimens such as BPaL (bedaquiline, pretomanid and linezolid) will provide evidence on the efficacy of the new drug, pretomanid, under these circumstances[14]. The prognosis of these patients is worse than in other forms of DR-TB.

CONCLUSIONS

In this brief review of the practical pharmacological aspects of drugs for the treatment of DR-TB in adults and children, we show drugs (such as bedaquiline, delamanid and pretomanid) that have been specifically studied as antituberculosis drugs, something that hadn't occurred since the discovery of rifampicin, half a century ago. This is an auspicious fact, together with the evidence showing the activity of drugs that allow a 100% oral treatment in children and adults. There is availability of regimens based on published evidence for the treatment of monoresistant and multi-drug resistant TB. Unfortunately, XDR-TB, the most severe mycobacterial resistance situation, is still a complex problem in terms of therapeutic and prognostic aspects.

Conflict of interest

Authors declare there isn't any conflict of interest in relation to this publication.

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